Chronic obstructive pulmonary disease, pulmonary function and cardiovascular disease

David A McAllister

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Abstract

Cardiovascular disease is common in Chronic Obstructive Pulmonary Disease (COPD), and forced expiratory volume in one second (FEV_1) independently predicts cardiovascular morbidity and mortality. Pathological changes in the systemic vasculature have been proposed as potential mechanisms linking COPD to cardiovascular disease, and patients with COPD may be at increased risk of acute myocardial infarction during acute exacerbations. Notwithstanding causation, FEV_1 may be a useful prognostic marker in patients undergoing cardiac surgery. This thesis examined these three aspects of cardiovascular co-morbidity in relation to COPD and FEV_1.

In 2,241 consecutive cardiac surgery patients, FEV_1 was associated with length of hospital stay ($p<0.001$) and mortality ($p<0.001$) adjusting for age, sex, height, body mass index, socioeconomic status, smoking, cardiovascular risk factors, chronic pulmonary disease, and type/urgency of surgery.

In a survey of Scottish Respiratory Consultants there was no consensus regarding the investigation and management of acute coronary syndrome in exacerbation of COPD. In a case-series of 242 patients with exacerbations 2.5% (95% CI 1.0 to 5.6%) had chest pain, raised serum troponin and serial electrocardiogram changes suggestive of acute coronary syndrome. However, over half reported chest pain, while raised troponin was not associated with chest pain or serial ECG changes.

Carotid-radial pulse wave velocity (PWV), aortic distensibility, and aortic calcification were measured to assess the relationship of the systemic vasculature to FEV_1 and emphysema severity on CT. In adjusted analyses, emphysema was associated with PWV in patients with COPD ($p = 0.006$) and, in population based samples, with extent of distal aortic calcification ($p=0.02$) but not with aortic distensibility ($p=0.60$).

This thesis found that FEV_1 was associated with mortality and length of hospital stay in patients undergoing cardiac surgery, and that chest pain and raised troponin were common but unrelated in exacerbation of COPD. In the vascular studies distal but not proximal vascular pathology was associated with FEV_1, and if COPD is truly related to systemic arterial disease, the distal arterial tree is implicated.

Declaration

I declare that I wrote this thesis and the work presented was my own, with the exceptions listed below:

i. All the data used in Chapter 2 was collected as part of routine clinical care. The data analysed in Chapters 5 through 7 were collected as part of larger National Institutes of Health funded studies and as such the initial study design, data collection and validation were performed by numerous other clinicians, scientists, administrative and technical staff.

ii. Patient history taking, electrocardiography and venepuncture at sites other than Lothian were performed by Drs Andrew Leitch, Dr Phillip Reid and Dr Jen O'Conner and, in a small proportion of patients recruited at Lothian, by medical students under my direct supervision.

I declare that this work has not been submitted for any other degree. The dataset used in Chapter 2 had originally been created by record linkage, and was used to test the hypothesis that FEV1 is related to atheroma burden on coronary angiography as part of a dissertation submitted for an MSc in Public Health Research. The research question addressed in this thesis is entirely separate.

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Relevant publications, presentations and awards

Papers

McAllister DA, Maclay JD, Mills NL, Mair G, Miller J, Anderson D, Newby DE, Murchison JT, MacNee W. Arterial stiffness is independently associated with emphysema severity in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2007 Dec 15;176(12):1208-14.

Maclay JD, McAllister DA, Mills NL, et al. Vascular Dysfunction in Chronic Obstructive Pulmonary Disease. Am J Respir Crit Care Med. 2009;180(6):513-520.

MacNee W, Maclay J, McAllister D. Cardiovascular Injury and Repair in Chronic Obstructive Pulmonary Disease. Proc Am Thorac Soc. 2008 Dec 1;5(8):824-833. *Review*

Maclay JD, McAllister DA, MacNee W. Cardiovascular risk in chronic obstructive pulmonary disease. Respirology. 2007 Sep;12(5):634-41. *Review.*

Abstracts

McAllister DA et al. Aortic Distensibility Is Not Associated with Lung Function or CT Percent Low Attenuation Area in Participants without Clinical Cardiovascular Disease. The MESA-Lung Study, [Publication Page: A4026]. American Thoracic Society International Conference 2009.

McAllister DA et al. Coronary Atheroma Burden Is Not Associated with FEV1 in Cardiac Surgery Patients, [Publication Page: A4032]. American Thoracic Society Conference 2009.

McAllister DA et al. Arterial Stiffness Is Associated with Emphysema Severity, [Publication Page: A783]. American Thoracic Society International Conference 2008.

McAllister DA et al. Acute coronary events during acute exacerbations of chronic obstructive pulmonary disease European respiratory Society Annual Congress 2007.

Presentations

Aortic Distensibility Is Not Associated with Lung Function or CT Percent Low Attenuation Area in Participants without Clinical Cardiovascular Disease. Poster Discussion Session. American Thoracic Society International Conference 2009.

Coronary Atheroma Burden Is Not Associated with FEV1 in Cardiac Surgery Patients. American Thoracic Society International Conference 2009.

Arterial Stiffness Is Associated with Emphysema Severity. Poster Discussion Session. American Thoracic Society International Conference 2008.

Endothelial Vasomotor Function is not Impaired in COPD. Poster Discussion Session. American Thoracic Society International Conference 2008.

Chest Pain, Raised Troponin and ECG changes in Acute Exacerbation of COPD. Oral Presentation. European Respiratory Society Conference 2007.

Arterial Stiffness is Associated with Emphysema Severity. Oral Presentation. British Thoracic Society Winter Conference 2007.

Book chapters

McAllister DA, Maclay JD, Rabinovitch R, MacNee W. Comorbidity at AECOPD in Chronic Obstructive Pulmonary Disease Exacerbations, Editors Wedzicha and Martinez. Informa Healthcare 52 Vanderbilt Avenue. New York, NY 10017 U.S.A.

Awards

Chest, Heart and Stroke Scotland Fellowship. 2007.

American Thoracic Society Travel Award. National Emphysema Foundation. 2009.

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List of abbreviations

ABI	Ankle brachial index
ABPI	Ankle brachial pressure index
ACC	American College of Cardiology
ACE	Angiotensin converting enzyme
ANOVA	analysis of variance
ARIC	Atherosclerosis Risk in Communities Study
ATS	American Thoracic Society
AUC	Area under the curve
BMI	Body mass index
BTS	British Thoracic Society
CABG	Coronary artery bypass graft
CHD	Coronary heart disease
CIIS	Cardiac Injury Infarction Score
CIMT	Carotid intimal medial thickness
COPD	Chronic obstructive pulmonary disease
CRP	C-reactive protein
EBT	Electron beam tomography
ECG	Electrocardiogram
ERS	European Respiratory Society
ESC	European Society of Cardiology
FEV_1	Forced expiratory volume in one second
FMD	Flow mediated dilation
FVC	Forced vital capacity
GOLD	Global initiative on obstructive lung disease

HDL	High density lipoprotein
ICC	Intra-class correlation co-efficient
IDI	Integrated discrimination index
IHD	Ischaemic heart disease
Il-6	Interleukin 6
IMT	Intimal medial thickness
IMTcca	Intimal medial thickness common carotid artery
IMTbif	Intimal medial thickness bifurcation of the carotid artery
IQR	Interquartile range
IRR	Incidence rate ratio
ISD	Information Service Division
LBBB	Left bundle branch block
LDL	Low density lipoprotein
LLD	Lower limit of detection
LLN	Lower limit of normal
LOS	length of stay
MDCT	Multi-detector computed tomography
MESA	Multi Ethnic Study of Atherosclerosis
mmHg	Milimetres of mercury
MMP	Matrix metalloproteinase
MRC	Medical Research Council
MRI	Magnetic resonance imaging
NHANES	National Health and Nutrition Examination Survey
NICE	National Institute for Clinical Excellence
NRI	Net reclassification index

NYHA	New York Heart Association
OR	Odds ratio
PEFR	Peak expiratory flow rate
PWV	Pulse wave velocity
RBBB	Right bundle branch block
SGRQ	St George's Respiratory Questionnaire
SIMD	Scottish Index of Multiple Deprivation
TIA	Transient ischaemic attack
TNF-α	Tumour necrosing factor alpha
WCC	White cell count

1. Introduction

1.1. COPD, definition and prevalence

Over the past 10 years two major international guidelines and a national guideline have been produced for Chronic Obstructive Pulmonary Disease (COPD) by the American Thoracic Society/European Respiratory Society (ATS/ERS) (American Thoracic Society/European Respiratory Society 2004), the Global Initiative on Obstructive Lung Disease (GOLD) (Gold Executive Committee 2008), and the National Institute of Clinical Excellence (NICE) (NICE 2004). All three have provided definitions of the disease (Table 1-1). The presence of spirometry consistent with airflow limitation (forced expiratory volume in one second/forced vital capacity (FEV_1/FVC) ratio <0.7) which does not fully reverse to normal lung function following bronchodilator administration is crucial to all three diagnoses, and each additionally states that airflow limitation is generally progressive in patients with COPD. The NICE guidelines definition does not require the administration of a bronchodilator before spirometry, but does have the additional criterion of FEV_1 percent predicted <80%. The central role of smoking as the cause of COPD is emphasised in the NICE and ATS/ERS guidelines, and to a lesser extent in the GOLD guidelines.

In an international cross-sectional study which employed random sampling methods to obtain population-based samples (n=9425, 12 sites), the prevalence of COPD defined as GOLD stage II (FEV_1/FVC <0.7 and FEV_1 percent predicted <80%) in individuals aged 40 or over was 11.8% for men and 8.5% for women (Buist et al. 2007). Conservatively, this definition did not include all individuals with FEV_1/FVC <0.7, which some authors have suggested leads to over diagnosis of COPD in older people (Hardie et al. 2002).

Both GOLD and the ATS/ERS mentioned 'extra-pulmonary' or systemic ‘manifestations’ in their definitions of COPD, reflecting the considerable recent interest in ‘co-morbidity’ in patients with COPD (Fabbri et al. 2008) from diseases such as osteoporosis, coronary heart disease, and from skeletal muscle dysfunction. Amongst these, cardiovascular disease has received particular attention.

Table 1-1 Definitions of COPD

Guideline body	Excerpt of guideline
American Thoracic Society/European Respiratory Society 2004	Chronic obstructive pulmonary disease (COPD) is a preventable and treatable disease state characterised by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and is associated with an abnormal inflammatory response of the lungs to noxious particles or gases, primarily caused by cigarette smoking. Although COPD affects the lungs, it also produces significant systemic consequences. The diagnosis requires spirometry; post-bronchodilator $FEV_1/FVC < 0.7$ confirms the presence of airflow limitation that is not fully reversible.
Gold Executive Committee 2008	COPD is a preventable and treatable disease with some significant extra-pulmonary effects that may contribute to the severity in individual patients. Its pulmonary component is characterised by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response in the lung to noxious particles or gases. Spirometry is essential … post-bronchodilator FEV_1/FVC ratio <0.70.
NICE 2004	Chronic obstructive pulmonary disease (COPD) is characterised by airflow limitation (FEV_1 <80% predicted and $FEV_1/FVC < 0.7$). The airflow limitation is usually progressive, not fully reversible and does not change markedly over several months. The disease is predominantly caused by smoking.

1.2. FEV_1, COPD and cardiovascular risk

1.2.1. Cardiovascular mortality and morbidity are common in COPD

A review of 130,000 death certificates from 1993 to 1999 in England and Wales found that, where obstructive lung disease was mentioned, ischaemic heart disease was recorded as the underlying cause of death in approximately 25% of cases (Hansell et al. 2003). In a similar design in a French population in the period from 2000 to 2002, cardiovascular diseases were found in 32% of death certificates where COPD was also mentioned, compared to 22% where it was not (relative risk (RR) 1.49; 95% CI 1.46 to 1.52) (Fuhrman et al. 2006). In the Tucson Epidemiologic Study of Airways Obstructive Disease 47% of men and 63% of women in whom obstructive airways disease was mentioned as a contributing cause of death had a circulatory disease as the primary cause of death (Camilli et al. 1991). The Lung Health Study recruited 5,887 smokers aged 35 to 46 with airflow limitation ($FEV_1/FVC \leq 75\%$ and FEV_1 percent predicted from 50 to 90%) and reported deaths and hospitalisations at 5 years follow-up. 149 participants died and 754 were hospitalised one or more times (Anthonisen et al. 2002). All deaths and all hospitalisations where the hospital records made a significant mention of respiratory or cardiovascular disease or cancer were independently reviewed by the study's mortality and morbidity review board. Twenty-five percent of deaths were due to a cardiovascular event, and cardiovascular disease accounted for 42% of first hospitalisations, whereas 14% of hospitalisations were due to respiratory causes. In a recent clinical trial of inhaled corticosteroids/long acting beta agonists in 8,184 participants with moderate to severe COPD (FEV_1 percent predicted <60%) members of a clinical endpoint committee independently adjudicated the cause of death in 911 cases, and found that 27% of all deaths were due to cardiovascular disease (McGarvey et al. 2007). Therefore, cardiovascular morbidity and mortality are common in patients with COPD.

1.2.2. A diagnosis of COPD is associated with increased cardiovascular mortality and morbidity

Evidence from secondary analyses of healthcare databases suggests that COPD may be a risk factor for increased cardiovascular morbidity and mortality.

In a study using the Saskatchewan healthcare database, COPD (n=11,493, defined on the basis of inhaled bronchodilator prescription in persons aged 40 or older) diagnosed from 1997-2000 was associated with a higher risk of hospitalisation with a cardiovascular event (risk ratio 1.17; 95% CI 2.00 to 2.33) after adjusting for cardiovascular events, diabetes, hypertension, and hypercholesterolemia compared to controls matched on age and sex (n=22,986) (Curkendall et al. 2006). In a similar study published a year earlier also using the Saskatchewan database, but in the period from 1990 to 2007, a diagnosis of COPD (defined on the basis of treatment with inhalers or methylxanthines) was also associated with an increased risk of hospitalisation (RR 1.89; 95% CI 1.83 to 1.94, adjusting for age, sex and calendar year) and mortality (standardised mortality ratio 1.95; 95% CI 1.83 to 2.07) from cardiovascular disease compared to the general Saskatchewan population (Huiart et al. 2005).

Similarly, a retrospective matched cohort study Sidney et al. (2005) examined associations between diagnosis with COPD (defined on the basis of COPD code on discharge, and two prescriptions for inhaled bronchodilator therapy) using a database from a prepaid integrated health-care system in California. Controls were matched on gender, year of birth, length of membership in scheme, and the analyses adjusted for age, gender, hypertension, hyperlipidemia, diabetes, and previous coronary heart disease. COPD predicted increased risk of hospitalisation (RR 1.87; 95% CI 1.69 to 2.08) and death (RR 1.85; 95% CI 1.55 to 2.21) from myocardial infarction.

However, these studies obtained morbidity and mortality data from routine sources such as death certificates, which can lead to diagnostic misclassification. Moreover, data on smoking and other potential confounders was either absent or incomplete which may have resulted in confounding. More crucially, patients given a diagnosis of COPD are likely to differ from those not diagnosed with COPD in terms of socioeconomic status, access to and use of healthcare and presence of co-morbid disease, which means the observed associations could have arisen from selection bias.

1.2.3. Reduced FEV_1 is a predictor of increased cardiovascular mortality

Nevertheless, FEV_1, which is reduced in COPD, has been found to predict cardiovascular mortality in a number of longitudinal analyses from cohorts widely dispersed in time and place. A recent systematic review of longitudinal studies summarised results from studies with 500 or more subjects in which FEV_1 and cardiovascular mortality was reported (Sin et al. 2005). Twelve studies met pre-specified quality criteria (of 30 meeting the inclusion and exclusion criteria, from 340 initially identified) comprising a total of 83,880 individuals. The reports were published over three decades from 1970 to 2000, and presented data obtained in the UK, the US and continental Europe. All twelve found that low FEV_1 predicted cardiovascular mortality, and in a meta-analysis the pooled estimate for the relative risk of cardiovascular disease for those in the group with the lowest lung function compared to those in the group with the highest lung function was 1.99 (95% CI 1.71 to 2.29). The various studies used a variety of analytical strategies, and statistical adjustment was made for a range of potential confounding factors including age, gender, race/ethnicity, socioeconomic status, smoking status, smoking pack years, blood pressure, diabetes, cholesterol, and patient medications. Similar associations have also been described for the peak expiratory flow rate another marker of lung function (Persson et al. 1986).

Estimates of the proportion of smokers who develop abnormal lung function vary (Lundback et al. 2003), but smoking causes both impaired lung function (Scanlon et al. 2000) and coronary heart disease (Kawachi et al. 1994). Smoking is therefore likely to at least partly confound any association between FEV_1 and cardiovascular disease. Unsurprisingly, each study of lung function and coronary heart disease adjusted for smoking. However, exposure to cigarette smoke is difficult to measure. Indeed, the best established measure of exposure, pack years (pack years = number of years smoked x no. of cigarettes smoked per day / 20) is based upon individual patient recall, and takes no account of the amount of smoke inhaled per cigarette. As such, a plausible explanation for any association between FEV_1 and cardiovascular risk is residual confounding from cigarette smoke exposure. Nevertheless, FEV_1 also appears to predict cardiovascular mortality amongst never smokers, defined as

individuals who have smoked less than 100 cigarettes in their lifetime (Hole et al. 1996; Strachan 1992) suggesting that the association between FEV_1 and cardiovascular disease may be genuinely independent of the effects of cigarette smoke exposure.

Therefore, since COPD is the commonest cause of reduced FEV_1 in adults, evidence from population-based studies support the view that cardiovascular risk is increased in COPD, independently of established cardiovascular risk factors.

However, in population-based studies adjusting for potential confounders, FEV_1 is associated with ischaemic heart disease mortality in a broadly linear fashion. In the Midspan study the relative risk in quintiles one though four compared to the fifth quintile were 1.56, 1.48, 1.55 and 1.15 respectively for men, and 1.88, 1.50, 1.22 and 1.01 respectively for women (Hole et al. 1996). Similarly, in the NHANES cohort, in quintiles one though four compared to the fifth quintile the relative risk of mortality from ischaemic heart disease was 5.65, 3.11, 3.69 and 1.50 respectively (Sin et al. 2005). Therefore, there was no threshold above which higher FEV_1 did not predict a lower risk of adverse outcomes, which suggests that FEV_1 may be a broad marker of cardiovascular risk, rather than that COPD is a specific cause of cardiovascular disease.

Nevertheless, on a population scale the magnitude of the association between FEV_1 and cardiovascular risk is considerable. Indeed, in the Midspan study the population attributable of risk (PAR) of death from coronary heart disease associated with being in the lowest quintile of FEV_1 percent predicted compared to the highest quintile of FEV_1 percent predicted was 26.2; 95% CI 18.6 to 33.8 for men, and 23.9; 95% CI 13.8 to 34.0 for women. This PAR was similar to that obtained for elevated serum cholesterol for men (PAR 20.5; 95%CI 12.8 to 28.2) and women (PAR 24.8; 95% CI 14.9 to 34.7) (Hole et al. 1996).

1.3. Mechanisms linking FEV_1/COPD and cardiovascular risk

The potential relevance of the complex relationships between impaired pulmonary function, COPD, cigarette smoke exposure and other environmental pollutants and co-morbid disease was discussed in an editorial as early as 1978 (Cohen 1978).

Despite this the mechanisms underlying the association between FEV_1 and cardiovascular disease have not been extensively studied. FEV_1 and COPD might cause or be associated with any of several steps on the pathway towards clinical cardiovascular disease; i.e. the formation and development of atheromatous plaques, plaque rupture, thrombus formation, myocardial cell death, clinical morbidity (angina, heart failure, arrhythmia etc) and death, or with diagnostic activity.

One reason for this relative inattention is that FEV_1 is not specific to cardiovascular disease, and predicts a broad range of adverse health outcomes including cancer from all causes, non-respiratory cancer, rupture of aortic aneurysm, and psychiatric illness (Pembroke et al. 2006; Hole et al. 1996; Brown & Powell 1999). Therefore, FEV_1 may be a broad marker of poor health, making it less likely that it is a cause of cardiovascular morbidity and mortality.

However, more recently several authors have proposed that potentially modifiable biological mechanisms may explain the association between COPD and cardiovascular disease, including endothelial dysfunction, systemic inflammation, alteration in platelet function and clotting factors, and a systemic susceptibility in the connective tissues causing both emphysema and vascular disease (Sin & Man 2003; MacNee et al. 2008).

1.4. Atheroma and arterial stiffness

1.4.1. FEV_1 and COPD and associations with atheroma

Several studies have examined associations between atheroma and FEV_1, using a variety of methods, including ultrasound which can measure intimal medial thickness and plaque thickness (usually defined as localised areas of thickness >1mm or >1.5mm), doppler ultrasound which measures stenosis, ankle-arm pressure index (pressure transducers at toe and thumb) and ankle-brachial index (sphygmomanometer measures pressure at brachial artery and ankles), lower pressures in the lower limbs implies stenosis in arteries supplying the lower limbs, calcium scoring (wherein calcium detected on CT scan is quantified and regions of calcification are proxies for calcified atherosclerotic plaques, and coronary angiography (wherein the coronary artery is cannulated radio-opaque dye is injected

and x-ray screening is used to identify coronary artery anatomy and regions of stenosis and occlusion).

In a cross-sectional study Ebrahim et al. (1999) measured plaque burden via B-mode ultrasound at the common carotid artery (IMTcca) and at the bifurcation of the carotid artery (IMTbif). The 425 men sampled were selected from the British Regional Heart Study cohort, and the 375 women were selected from a random sample of the age-sex register of general practices (the sampling frame from which the British Regional Heart Study was originally drawn). Response rates were 83% for men and 69% for women. In an analysis adjusting for age, height-standardised FEV_1 (categorised in tertiles) was statistically significantly inversely associated with IMTcca in men and women ($p<0.05$), and IMTbif was higher in men in the lowest tertile for height-standardised FEV_1, although this was not statistically significant (confidence intervals not provided). There was no association with the presence of carotid plaques, but the confidence intervals were broad (in men odds ratio 0.72; 95% CI 0.4 to 1.2). The intra and inter observer reproducibility of the ultrasound measurement of IMT and plaque thickness was good, but the measurement was not blinded. Furthermore, spirometry is technically difficult to perform, and quality control measures were not reported. Moreover, neither adjustment nor stratification was used to control for confounding by cigarette smoke exposure.

In 220 male smokers from a 1914 Swedish Birth Cohort Engström et al. (2001) tested for an association between FEV_1 aged 55 and 65, and the presence of sub-clinical leg or carotid atheroma aged 68 (composite endpoint). FEV_1 was measured via spirometry when the men were aged 55 and again aged 68 and was standardised by height on both occasions. Atheroma was measured indirectly at both sites at age 68. Carotid stenosis was assessed using doppler ultrasound, and leg atheroma was measured using the systolic ankle–arm pressure index. After adjusting for current tobacco consumption aged 55 and 68, hypertension (high blood pressure), diabetes and alcohol consumption aged 68, the authors found associations between height-standardised FEV_1 aged 55 and aged 68 and presence of atheroma aged 68 (0.5 litre increase in FEV_1; OR 0.76 (95%CI 0.57 to 0.998), and OR 0.79 (95%CI 0.62 to 0.998) respectively). Similar associations were found for FVC. The authors concluded that the association was unlikely to be due to confounding by smoking.

However, residual confounding by smoking appears probable since only smoking status, and not lifetime cigarette smoke exposure was measured. Moreover, only 220 of the 389 smokers originally enrolled had their plaque burden assessed aged 68 (due to deaths, emigration, refusals etc) so selection bias may also account for the association. Furthermore, there was no record of whether those assessing plaque burden were blinded to the lung function results.

In the largest study to examine this question Schroeder et al. (2005) examined lung function and markers of plaque burden in 14,480 participants obtained by probability sampling in the Atherosclerosis Risk in Communities (ARIC) Study. Carotid atheroma was measured as carotid intimal medial thickness via B-mode ultrasound, and carotid plaque was identified as wall thickness >1.5mm and other criteria. Atheroma in the leg was identified via the ankle brachial index (ABI). All measurements, including spirometry were performed to a high standard. Crucially, Schroeder et al. stratified by smoking status and reported associations amongst never smokers. FEV_1 was associated with atheroma burden in the leg measured via ABI, even amongst never smokers and after adjusting for age, gender, race, study centre, height, height-squared, and established cardiovascular risk factors (FEV_1 was 2.97 litres, 95%CI 2.95 to 2.98, in the 'lowest' plaque burden group and was 2.83 litres, 95%CI 2.83 to 2.95, in the 'highest' plaque burden group).

The only longitudinal study found was published by (Zureik, Kauffmann, et al. 2001). 1389 participants aged 59 to 71 were recruited in Western France from the electoral register without random sampling and through advertising (Bonithon-Kopp et al. 1996). From among this group, 656 individuals had Peak Expiratory Flow Rate (PEFR) measurement and carotid B-mode ultrasound performed at baseline, and after 2 and 4 years. PEFR is an alternative measure of lung function which can be performed more quickly using more portable equipment than spirometry, and is itself a predictor of cardiovascular mortality (Persson et al. 1986). In this study, PEFR was standardised by age and height using sex-specific reference equations (relative PEFR). Of 656 subjects, 110 had incident carotid plaque disease, defined as the presence of a new lesion which was 1mm or thicker, encroaching onto the vessel lumen. Incident cases were defined as individuals with new plaques, even if plaques were already present at other sites on the artery wall.

In logistic regression models low relative peak flow at baseline was associated with incident plaque burden (lowest quintile of peak flow compared to highest quintile, (OR 3.07; 95% CI 1.62 to 5.85, follow-up period was 4 years). This association persisted after adjustment for age, sex, body mass index, hypertension, hypercholesterolemia, diabetes, smoking habits, alcohol consumption, common carotid artery intima-media thickness, and the presence of carotid plaques at baseline (OR 2.84; 95% CI 1.45 to 5.71).

The longitudinal design may partly account for the effect of potential unmeasured confounders. In addition, the authors performed a range of sensitivity and sub-group analyses, including amongst never smokers, to which the findings proved robust. Surprisingly however, there was no association between baseline plaque disease and baseline relative peak flow, and only a small difference in CIMT between the highest and lowest quintiles. Furthermore, it is not biologically plausible that low PEFR could cause (or be a consistent marker of the risk of) new atheromatous plaque formation aged 60 over a 4 year period. As such, the reported association may well have been a chance finding, or the consequence of observer bias, particularly as the ultrasound assessments of plaque burden were not blinded, and there is considerable subjectivity in the measurement of plaque burden the authors employed.

In January 2009 a case-control study was published, in which healthy Japanese men presenting at an occupational health service had been recruited (Iwamoto et al. 2009). From 2,037 attendees the authors identified 1,054 subjects without diabetes, impaired glucose tolerance or respiratory diseases (other than COPD). From among the 1,054, the authors selected sixty-one cases with airflow limitation on spirometry and a history of smoking of ten or more pack years. Each participant was individually matched to four controls without airflow limitation, two smokers and two non-smokers. B-mode ultrasound was used to measure carotid IMT, and the authors defined atheromatous plaque disease as a localised area of thickness greater than 1.5mm. The authors found that carotid intimal medial thickness was increased in the group with airflow limitation (0.78mm in cases, and 0.73 mm in each of the control groups, $p<0.01$, confidence intervals not presented). They also found that plaques were commoner amongst smokers with airflow limitation. There were a number of strengths in this study, including the fact that cases and controls were

obtained from the same sampling frame, and that the ultrasonographer was blinded to the subjects status as case or control.

However, the statistical analysis did not take into account the fact that the cases and controls were individually matched. Use of an unconditional analysis is likely to produce wider standard errors than a conditional one, but may also overestimate the effect size. Similarly, the authors attempted to adjust for differences in a variety of potential confounders (eg high cholesterol) using linear and logistic regression, but did so using stepwise methods, which may have missed important confounders.

Unlike the carotid arteries, the coronary arteries cannot be readily assessed using ultrasound techniques, and invasive or radiation-based methods are needed to assess the plaque burden. Four studies were found which examined these measures, two of which were published only in abstract form.

Barr et al. (2007) examined the association between FEV_1 and the coronary arteries, in The Multi Ethnic Study of Atherosclerosis (MESA). MESA used random telephone number dialling to recruit individuals from six US communities. Individuals with clinically evident coronary heart disease were excluded from the study. Coronary artery plaque burden was measured using coronary artery calcium scoring, and carotid artery plaque burden was measured using carotid IMT via ultrasound. Lung function was measured using spirometry to determine FEV_1 and FVC. A wide range of potential confounders were measured. In 3,226 individuals, IMT at the internal carotid artery was inversely associated with FEV_1 (1.28 mm thick in the group with worst lung function, compared to 1.03 mm thick in the group with the best lung function, $p<0.001$, no confidence interval presented). However, after adjusting for age, sex, race, education, smoking, pack years, body mass index, diabetes, fasting plasma glucose, hypertension, systolic and diastolic blood pressure, low density lipoprotein, high density lipoprotein, and C-reactive protein (CRP), only a weak association was found ($p=0.05$). Furthermore, there was no evidence of an association between coronary artery calcium score and low FEV_1 ($p=0.86$, no confidence interval presented). It is difficult to assess the quality of this work from an abstract presentation. However, the sample used was drawn using probability sampling from a relevant population, the measures of plaque burden were performed

blind and to a high technical standard, and the authors adjusted for a wide range of possible confounders. Nevertheless, the restriction to individuals without clinical cardiovascular disease may have caused the investigators to miss an important association.

In a retrospective chart review in 1720 consecutive patients who self-presented at a cardiac imaging centre coronary artery calcium measures and lung images were obtained using electron beam computed tomography scans. Seventy-eight (5%) of patients had emphysema identified qualitatively on CT scan, and raised coronary artery calcium was commoner in this group than in the remaining 1642 patients without emphysema on CT scan (31% vs 19%, p=0.01). However, although age, sex, hypertension and smoking status were independently associated with having a raised coronary artery calcification score, emphysema on CT scan was not (Alhaj et al. 2008).

In work submitted for an MSc dissertation, published solely in abstract form (McAllister et al. 2009), I examined whether FEV_1 was associated with the Gensini score, a quantitative score of plaque burden derived from coronary angiography (Gensini 1983). 2,241 patients were identified in the Lothian Cardiac Surgery Database aged>40 years who had surgery from 2001 to 2007. Using name, date of birth, and postcode these cases were linked to local spirometry and angiography databases. Spirometry and angiography records were available for 93.2% and 93% of cases respectively. Following angiography the degree of stenosis in 14 epicardial arterial segments, estimated visually, is recorded. After excluding patients with restrictive spirometry (n=234) FEV_1 was not associated with Gensini Score after adjusting for age, sex, height and weight (n=1709, 0.02 ml; 95% CI -0.62 to 0.66 ml, p=0.95). Similar results were found after also adjusting for social class, smoking status, diabetes and hypertension, with alternative measures of coronary burden, and if FEV_1/FVC or FEV_1 percent predicted was used in place of FEV_1. These findings were consistent with those reported by Barr et al from the MESA study.

However, this was a secondary analysis of data obtained from a clinical sample. Sampling was not random, and selection bias is therefore an important consideration, particularly as both lung function and coronary angiography are likely

to be related to reasons for selection for surgery. There was no adjustment for pack years smoking, and therefore confounding was possible, but unlikely to account for the null association between FEV_1 and angiographic burden.

The most recent study examining the association between lung function and atheroma examined coronary artery calcification and FEV_1 using routine data in 4,905 men aged ≥ 40 (Park et al. 2009). In 2005-2008 6,446 men attending a health promotion centre for an annual health check were recruited, with 1,537 excluded because of a history of previous CHD, more than one attendance, or because metabolic/lung function measures were not performed/not available (n=79, 151, and 1,307 respectively). Coronary artery calcium scores were calculated using ECG gated scans from a single multidetector (MDCT) scanner (Philips, Brilliance 40). In analyses adjusting for age, smoking status and BMI participants in the lowest quartile of FVC percent predicted and FEV_1 percent predicted had higher odds of having any coronary calcification (Agaston score >0) than those in the highest quartile (OR 1.22; 95% CI 1.02 to 1.46, and OR 1.31; 95% CI 1.09 to 1.58 respectively).

Since almost a quarter of patients were excluded because of missing lung function/metabolic measures, selection bias might explain these findings, particularly since no details were provided as to how the excluded patients differed from those included in the main sample. More significantly, the study did not report findings for never smokers, or adjust for pack years smoke exposure, and therefore confounding by cigarette smoke exposure may explain the findings.

In summary, several studies have examined associations between FEV_1 or COPD and markers of atheroma, with variable results. Plaque burden measured at different sites and in different populations appears to have different associations with lung function. The strongest evidence was for atheroma in the arteries supplying the lower limbs, as a reduced ankle-brachial index was associated with FEV_1 even in never smokers after adjustment for a range of established cardiovascular risk factors. No published study appears to have imaged the aorta or iliac arteries and related calcification at these sites to FEV_1. Chapter 7 addresses this issue by examining associations between FEV_1, FVC and emphysema measures and calcification in the aorta from the proximal ascending aorta to the iliac arteries.

1.4.2. FEV_1 and COPD and associations with measures of arterial stiffness

Arterial stiffness can be measured at the local, regional and systemic level using a number of techniques (Laurent et al., on behalf of the European Network for Non-invasive Investigation of Large Arteries 2006). Local measures of arterial stiffness examine a particular site (e.g. the proximal 4 cm of the brachial artery) and can be obtained via both ultrasound and MR scanning, wherein the systolic and diastolic area are measured, and the difference is divided by the distending pressure to calculate the distensibility. Systemic measures of arterial stiffness can be derived from the pulse wave-form using a model of arterial function by obtaining a tracing of the radial pulse using a high sensitivity tonometer (e.g. the augmentation index (Atcor Medical 2008). Finally, regional arterial stiffness can be measured as the pulse wave velocity (PWV) across a vascular region (Figure 1-1).

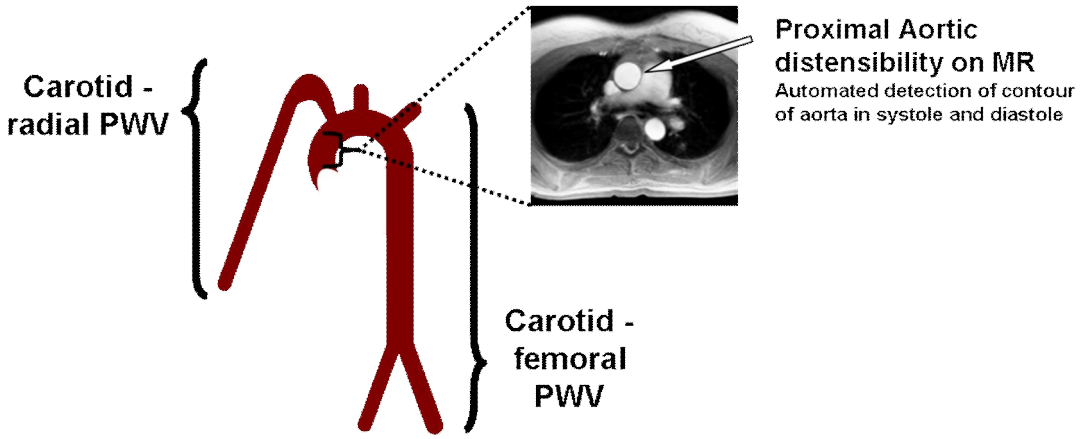

Figure 1-1 Selected arterial stiffness measures

The fact that pressure waves travel faster through stiffer materials than less stiff materials, and therefore that the speed of the arterial pressure wave is proportional to the arterial stiffness across each region, can be derived from Newton's second law of motion (Nichols & O'Rourke 1990) . PWV can be measured across several arterial regions, although only carotid-femoral PWV has been validated in longitudinal studies as a predictor of cardiovascular risk (Laurent et al., on behalf of the European Network for Non-invasive Investigation of Large Arteries 2006). Carotid-femoral PWV measures PWV across the thoracic and abdominal aorta and iliac artery, whereas carotid-radial PWV measures PWV across the aorta and brachial artery.

PWV can be measured using MR and ultrasound as well as by applanation tonometry but only the latter has been used in studies relating PWV to FEV_1 or COPD.

Measurement of applanation tonometry for carotid-radial PWV is illustrated in Figure 1-2. Briefly the length, along the body surface, between the sternal angle and the radial artery is measured, and the length from the sternal angle to the carotid artery, and the difference between the two is used to estimate the distance the wave travels between the heart and the site of the radial artery pulse. Similarly the difference in time is measured from the R-wave recorded on a simultaneous ECG to detection of the pressure wave at the carotid and radial pulses. The PWV is then calculated from these two measures. Carotid-femoral PWV is similar, except that the body surface measurement is made from the sternal angle to the femoral rather than the radial artery pulse, and the tonometer is placed at the femoral artery rather than the radial artery.

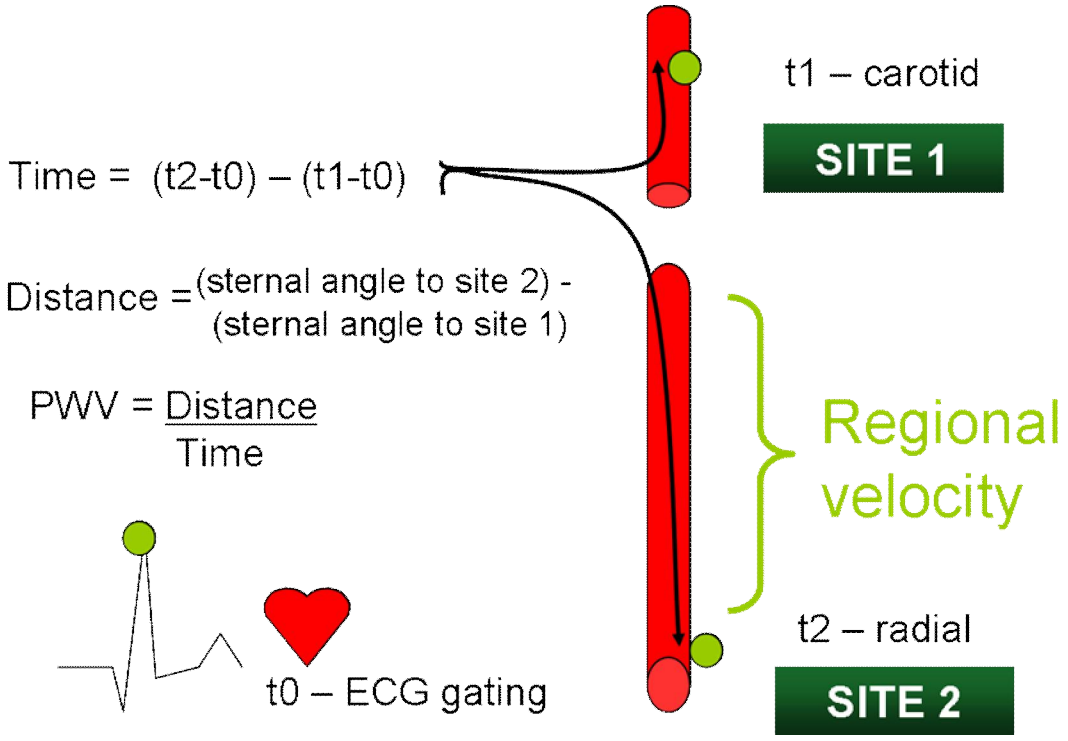

Figure 1-2 Carotid-radial PWV by applanation tonometry

Aortic distensibility can be measured via transthoracic ultrasound and by cardiac magnetic resonance (MR) and is a well-validated measure of local aortic stiffness (Oliver & Webb 2003). Aortic cross-sectional area is measured in systole and diastole, the distending pressure is measured or estimated, and the aortic

distensibility is calculated as 1000 x (maximum area – minimum area) / (minimum area x brachial pulse pressure).

Several measures of arterial stiffness (carotid-femoral PWV, aortic distensibility, and to a lesser extent carotid-radial PWV) have been associated with measures of coronary atheroma burden (coronary artery calcium scoring, coronary flow reserve and intravascular ultrasound)(Giannattasio et al. 2007; Gullu et al. 2006; Kullo et al. 2006; McLeod et al. 2004; van Popele et al. 2006), while both cardiac MR aortic distensibility and carotid-femoral PWV are associated with markers of endothelial dysfunction (Gullu et al. 2006; Newby et al., with McEniery et al., Yasmin 2006) and peripheral microvascular dysfunction (Cheung et al. 2007; Mitchell et al. 2005). Aortic stiffness is also believed to cause adverse physiological effects through increased central pulse pressure and increase left ventricular afterload (Laurent et al., on behalf of the European Network for Non-invasive Investigation of Large Arteries 2006).

Several studies have examined measures of arterial stiffness in relation to FEV_1 or COPD. Sabit et al reported that carotid-femoral PWV was higher in 74 patients with COPD than in 42 controls matched on age and sex (11.4 and 8.5 m/s respectively), and augmentation index (a systemic measure of arterial stiffness) was also higher (Sabit et al. 2007). However, the cases and controls differed in terms of current smoking (48% vs 14%) and lifelong smoke exposure (median 50 vs 15 pack years). Previous hypertension was also commoner in the COPD group (34% vs 21%). The recruitment of cases and controls was not described, and it may be that the observed differences are due to selection bias, particularly if cases were recruited from a population attending secondary care. The authors employed multiple linear regression, but the regression was performed across cases and controls without specifically modelling case/control status, and a stepwise approach was used rather than including potential confounders such as smoking status in the final model. As such, the differences Sabit et al observed in carotid-femoral PWV between cases and controls may be due to confounding from smoking status or lifelong cigarette smoke exposure, or previous hypertension, as well as from unmeasured confounders, as a result of selection bias.

Some of these deficiencies were addressed by Maclay et al in a case-control study in men, 19 with COPD and 17 controls, in which differences in carotid-femoral PWV of a similar magnitude were observed (11.2 and 9.2 respectively) (Maclay, McAllister, Mills, Paterson, et al. 2009). Inclusion was restricted to ex-smokers who had stopped for at least 3 months, without known cardiovascular disease (including hypertension) with a 10 or more pack year smoking history. Matching on pack years between cases and controls was close (median [IQR] 35 [35–48] and 34 [28–46] respectively).

However, both studies used case-control designs, and in neither study were cases and controls recruited from a sampling frame of a known population. Consequently, sampling bias might explain the differences between COPD patients and controls. Moreover, neither study employed blinding.

Nevertheless, two population based studies have reported an association between carotid-femoral PWV and reduced FEV_1, of which COPD is the commonest cause in older adults.

Zureik et al found that carotid-femoral PWV was associated with FEV_1 and FVC in men after adjusting for age, height, weight, diabetes, smoking status, hypertension and hypercholesterolaemia (2.5 m/s increment in PWV was associated with a 193ml decrement in FEV_1 and 158ml decrement in FVC (r^2=0.07, p <0.001 and r^2=0.05 p <0.006 respectively) (Zureik, Benetos, et al. 2001). The participants were recruited from one centre of a general health screening program offered to residents in Paris, France. The association between PWV and lung function was assessed using FEV_1 and FVC as continuous variables whereas potential confounders such as cholesterol and BP were dichotomised, which may have resulted in residual confounding. However, this is unlikely to account for the observed associations as adjusting for these dichotomous variables had minimal effect on the strength of association between FEV_1 and FVC and carotid-femoral PWV.

A key finding of Zureik et al was that FEV_1 and FVC had similar associations with PWV in a subgroup analysis of never smokers adjusting for the same covariates as in the main analysis (r^2=0.07 and r^2=0.04 respectively), although the definition of never smoker used by the authors was not provided.

Bolton et al also examined carotid-femoral PWV in a population-based sample of men (n=827) in Caerphilly in Wales, UK, finding that FEV_1 was associated with carotid-femoral PWV after adjusting for age group, height, mean arterial pressure, heart rate and smoking (beta-coefficient not given, $p < 0.001$) (Bolton et al. 2009). The authors found that adjusting for smoking status did not affect the strength of the association between FEV_1 and carotid-femoral PWV. The association was weaker in never-smokers but a global test for interaction with smoking status was not statistically significant (p-interaction >0.30, coefficients not provided).

In sub-group analyses Bolton et al additionally adjusted for early life factors (n=288, self-reported birth weight, childhood and adult socioeconomic status), systemic inflammation (n=211, CRP, blood viscosity and white cell count) and metabolic factors (n=313, body mass index, homeostasis model assessment (insulin resistance), serum triglycerides, and systolic blood pressure) in order to identify a mechanism linking FEV_1 and PWV. None of these variables attenuated the strength of the association between FEV_1 and PWV. However, as acknowledged by the authors, this may be due to deficiencies in the measures chosen, for example self-reported birth weight as a proxy for actual birth weight, rather than because none of these variables lie on the causal pathway.

However, in a study of 678 Japanese-Americans (male and female), Taneda et al found no association between carotid-femoral PWV and either FEV_1 or FVC, adjusting for age, sex, body mass index, total cholesterol/high density lipoprotein cholesterol ratio, hypertension, diabetes and smoking status (never, ex-smoker, or current) (Taneda et al. 2004). The authors dichotomised all exposures, outcomes and covariates, and the odds ratio for the association between high PWV and reduced FEV_1 percent predicted (<80%) was broad 1.39 (95% CI 0.82-2.34). However, although dichotomisation can reduce the power of an analysis, this cannot account for the lack of association as the findings were also null when PWV, FEV_1 and FVC were analysed as uncategorised raw values.

As such, the difference in findings between the European studies and that of Taneda et al may be due to differences in population, such as the low prevalence of current smoking (12%) or other differences in environmental exposures.

Alternatively, the different associations may reflect the different commercial tools used to measure PWV. Taneda et al used the PWV-200 velocimeter (Fukuda Denshi, Tokyo, Japan) while the European studies used the SphygmoCor device (AtCor Medical Pty Ltd., Sydney, Australia). The former device standardises the result to a diastolic blood pressure of 80mmHg while the latter does not. Nor is there any standardisation across devices, and they are likely to differ in their susceptibility to particular errors or biases (Xu 2003).

Systemic inflammation, endothelial dysfunction and systemic and pulmonary connective tissue susceptibility have all been proposed as mechanisms linking FEV_1 and COPD to measures of systemic vascular pathology such as arterial stiffness and atheroma.

1.4.3. Systemic inflammation and oxidative stress

Systemic inflammation is now a well established feature of reduced FEV_1 and of COPD. In a systematic review FEV_1 was associated with increased CRP, circulating platelets, leukocyte and fibrinogen (Sin & Man 2003), interleukin-6 (Il-6) (Walter et al. 2008) while Tumour Necrosing Factor alpha (TNF-α), CRP and oxidised lipids are increased in COPD (Gan et al. 2004; Santus et al. 2005). Spill-over from lung inflammation, hypoxia-induced production of inflammatory mediators and skeletal muscle dysfunction have been proposed as potential mechanisms for systemic inflammation and oxidative stress in COPD (Maclay et al. 2007).

The role of systemic inflammation as a causal factor in coronary heart disease remains controversial. In a meta-analysis of 22 population-based prospective studies CRP, which has been most extensively studied, was associated an increased risk of incident CHD (7068 cases, OR 1.6), and in animal models CRP has been implicated in plaque development, but genetic studies exploiting ‘Mendelian randomisation’ to examine the effect on CHD risk of single nucleotide polymorphisms known to increase CRP have so far had no association with coronary heart disease (Casas et al. 2008). However, these studies have been underpowered to detect moderate effects, and the effects of haplotypes for other inflammatory markers have not been investigated. Fibrinogen may be of particular interest, as it predicts longitudinal decline in lung function (Jiang et al. 2008).

Systemic inflammation is associated with arterial stiffness cross-sectionally, (Mahmud & Feely 2005) and predicts incident arterial stiffness longitudinally (Mattace-Raso et al. 2010), while TNF-α and oxidised lipids have been implicated in vascular calcification (Tintut et al. 2000; Parhami et al. 1997). Therefore systemic inflammation and oxidative stress is one possible mechanism linking FEV_1 and COPD with vascular pathology.

1.4.4. Endothelial dysfunction

Endothelial regulation of vascular smooth muscle cells acutely alters arterial stiffness, and endothelial dysfunction is associated with PWV and aortic distensibility (Gullu et al. 2006; Newby et al., with McEniery et al., Yasmin 2006). Endothelial dysfunction is also found with acute cigarette smoke exposure (Newby et al. 1999). Endothelial vasomotor function has been found to be impaired in patients with COPD compared to controls when measured via flow-mediated dilation (Eickhoff et al. 2008), but not via forearm plethysmography (Maclay, McAllister, Mills, Paterson, et al. 2009). In older former smokers flow-mediated dilation has also been found to be associated with FEV_1 and emphysema severity on CT scan (Barr, Mesia-Vela, et al. 2007).

Two competing hypotheses are found in the published literature concerning systemic endothelial dysfunction in COPD. Maclay and Eickhoff hypothesised that COPD causes increased systemic inflammatory markers which impair endothelial function, while Barr et al measured FMD in the systemic circulation as a marker of pulmonary endothelial function in order to test the hypothesis that cigarette smoke exposure causes emphysema and COPD through its effects on pulmonary endothelial cells. In the latter view systemic and pulmonary endothelial dysfunction are associated because both are affected by cigarette smoke exposure. Either mechanism could explain the observed associations between systemic vascular pathology and FEV_1 and COPD.

1.4.5. Connective tissue susceptibility

There are a number of pathological features common to arterial stiffness and emphysema which suggest that, in some individuals with COPD, there may be an acquired or inherited tendency to develop emphysema and arterial stiffness. Elastin

loss (Shifren & Mecham 2006), and increased alveolar septal thickening (Lang et al. 1994) occur in emphysema, while in stiff arteries elastin fragmentation is found, along with increased numbers of collagen fibres, and increased vessel lumen size and thickness (Zieman et al. 2005). In humans, a polymorphism in gelatinase B (MMP-9) is associated with increased risk of arterial stiffness (Medley et al. 2004; Zhou et al. 2007) as well as upper zone emphysema (Ito et al. 2005). In Marfan's syndrome increased aortic root stiffness is well described and has important clinical consequences, and people with Marfan's may also develop emphysema even in the absence of cigarette smoke exposure (Pyeritz 2000).

Increased levels of MMP-9 are found both in bronchoalveolar lavage (Finlay et al. 1997) and sputum (Boschetto et al. 2006) in subjects with emphysema, and levels of MMP-9 are increased in the serum of subjects with arterial stiffness (Wallace et al., with Yasmin 2005). MMP-12 (macrophage elastase) knockout mice are protected against cigarette smoke induced emphysema compared to wild-type mice (Hautamaki et al. 1997), and MMP-12/apoE deficient mice are protected against elastin degradation in atherosclerosis compared to single deficiency apoE mice (Luttun et al. 2004). Finally, the Klotho mouse (a model of accelerated ageing) develops early-emphysema, loss of skin elasticity and increased arterial stiffness (Kuro-o et al. 1997). Subjects with emphysematous phenotype of COPD may therefore have a systemic susceptibility to lung, skin, and arterial connective tissue damage.

Lung and artery susceptibility to connective tissue damage could be due to congenital variation in the synthesis, destruction and/or repair of extra cellular matrix. Unmeasured factors such as low birth weight, poor diet, recurrent infection, and environmental pollution might plausibly increase the susceptibility of both the lung and vasculature to connective tissue destruction, particularly in early life (Cheung et al. 2004; Martyn & Greenwald 1997; Kajekar 2007; Mills et al. 2005). Furthermore, recent evidence that COPD may have an autoimmune component characterised by an abnormal immune response to elastin (Lee et al. 2007) is of interest, as an autoimmune mechanism might explain associations between COPD, loss of skin elasticity and arterial stiffness.

1.5. Exacerbation of COPD and cardiovascular risk

1.5.1. Definition, incidence, pathophysiology and aetiology of exacerbations

There is no universally accepted clinical or pathological definition, but exacerbation of COPD has been defined pragmatically in statements by the National Institute for Clinical Excellence and the European Respiratory and American Thoracic Societies (NICE 2004; American Thoracic Society/European Respiratory Society 2004). These definitions are based upon a consensus definition reached at the 1999 Aspen Lung Conference in which European and American physicians arrived at a pragmatic definition of exacerbation of COPD as "a sustained worsening of the patient's condition, from the stable state and beyond normal day-to-day variation, that is acute in onset and necessitates a change in regular medication in a patient with underlying COPD" (Rodriguez-Roisin 2000). The ATS/ERS definition mirrors that of the Aspen conference, while the NICE guideline qualifies the statement on the necessity for treatment, instead stating that exacerbations 'often' require a change in treatment. Alternative definitions of exacerbation have been used in studies employing diary cards to identify exacerbations on a background of daily symptoms (Seemungal et al. 1998), and in studies focussed specifically on exacerbations of infectious aetiology (Anthonisen et al. 1987).

During acute exacerbations of COPD there is increased local and systemic inflammation and oxidative stress, increased airflow limitation as a result of mucosal oedema, mucus plugging and bronchospasm, dynamic hyperinflation, and hypoxaemia and acidosis (Fujimoto et al. 2005; Hurst et al. 2006; Praticò et al. 1998; O'Donnell & Parker 2006). The relative contribution of different pathogens and exposures to the aetiology of exacerbations remains controversial (Anzueto et al. 2007), although traditionally bacterial pathogens were believed to account for around 50% of exacerbations with the remainder being caused by viruses and air pollution (Sapey & Stockley 2006).

The reported incidence of exacerbations depends upon the definition employed and whether they are counted via diary cards, self-report, or from healthcare utilisation data. Nevertheless, exacerbations are a common cause of morbidity and mortality regardless of the methods used. According to data published by the Information

Services Division (ISD) of the National Health Service (http://www.isdscotland.org/isd/4334.html, Accessed June 2008) discharge from hospital in Lothian with a diagnosis of exacerbation of COPD was common with almost 5 exacerbations per 100 person years amongst men and women aged 65 to 74 (Table 1-2).

Exacerbations of COPD contribute to increased mortality and worse quality of life in patients with COPD (Soler-Cataluna et al. 2005; Seemungal et al. 1998)

Table 1-2 Discharges from hospital in Lothian with a diagnosis of exacerbation of COPD

	Year	n	Rate per 100,000 population
All Ages	2002/03	2648	340
	2003/04	3098	397
	2004/05	3024	384
	2005/06	2992	377
	2006/07	3396	424
Ages 65 to 74	2002/03	800	3383
	2003/04	959	4064
	2004/05	1026	4331
	2005/06	1023	4295
	2006/07	1129	4697

1.5.2. Exacerbations and cardiovascular risk

Although cardiovascular co-morbidity is common in COPD, the role of exacerbations has not been extensively studied, and published guidelines do not address whether and how patients with exacerbations of COPD should be

investigated or treated for acute cardiac disease (Gold Executive Committee 2008; American Thoracic Society/European Respiratory Society 2004; NICE 2004).

COPD and FEV_1 are both associated with increased cardiovascular risk (Sections 1.2.2 and 1.2.3). Evidence from two studies which performed secondary analyses of data obtained from healthcare databases suggest that the risk of myocardial infarction may be further increased during exacerbations in patients with COPD (Huiart et al. 2006; Donaldson et al. 2010).

Huiart et al identified a cohort of 5,658 patients with COPD on the basis of a minimum of 3 prescriptions within a 12-month period of inhaled oral beta-agonists, methylxanthines, or ipratropium from 1990 to 1997 from the Saskatchewan healthcare database. A nested case-control design was used to compare 371 cases with acute myocardial infarction to 1,864 controls. Using acute oral corticosteroid prescription as a proxy for acute exacerbation of COPD, Huiart et al found that exposure to oral corticosteroid therapy within the past 14 days was associated with an increased odds ratio for acute myocardial infarction (OR 2.01; 95% CI 1.13 to 3.58) adjusting or matching for age, duration of disease, sex, number of prescriptions of bronchodilators, inhaled corticosteroid use, hospitalisation within the past 3 months, diabetes, hypertension, known ischaemic heart disease and heart failure. The highest odds ratio was found with prescriptions of steroids equivalent to 25mg of prednisolone or more daily (OR 3.22). Oral steroid prescription within the previous 15 to 60 day period was not associated with an increased risk of myocardial infarction.

This study used routine data and did not report the results of any validation or quality control making coding errors likely. If non-differential then any such errors in the outcomes or exposures would tend to bias the effect estimates towards the null, but non-differential errors in the covariates can cause residual confounding. More importantly, the authors did not adjust for current smoking status, pack years or FEV_1 and therefore unmeasured confounding may explain the finding that exacerbations were associated with increased risk of myocardial infarction. Moreover, given the short duration between exposure and outcome, symptoms from unstable angina leading up to acute myocardial infarction may have been

misdiagnosed as exacerbation of COPD. The resulting misclassification would tend to produce a spurious correlation between exacerbations and myocardial infarction.

Donaldson et al identified 25,857 patients with COPD from a UK primary care database using Quality and Outcomes Framework codes (a healthcare management tool). Myocardial infarction was defined a priori on the basis of Read codes (coding system used in primary care throughout the UK) and there were 1.1 cases per 100 patient years. Three definitions were used for exacerbations on the basis of acute prescriptions (1) oral coroticosteroids >20mg/day, (2) selected antibiotics (penicillins, cephalosporins, tetracyclines, macrolides, sulphonamides and quinolones) and (3) both (1) and (2).

In a self-controlled case series design, conditional Poisson regression was used to estimate incidence rate ratios (IRRs). There was no association in the "high-risk" period of 7 weeks (49 days) post exacerbation, which had been chosen a priori, for any of the definitions of exacerbation (all definitions $p>0.45$). However, using exacerbation definition 3 (both steroid and antibiotic prescription) the 1 to 5 day period post-exacerbation period was associated with increased risk of myocardial infarction (IRR 2.27; 95% CI 1.1 to 4.7, $p=0.03$), with the other two definitions having weaker associations in the same direction which were not statistically significant (antibiotics IRR 1.14; 95% CI 0.7 to 1.8, $p=0.57$, steroids IRR 1.55; 95% CI 0.9 to 2.8; $p=0.15$).

Since Donaldson et al used a study design where each patient acted as their own control, the issue of confounding was adequately addressed. However, as routine data were used misclassification between exacerbations and myocardial infarction remains an issue, particularly as the diagnoses of exacerbation were made in primary care, where fewer clinical investigations are available. A further possibility is that this was a Type 1 error, particularly since risk of myocardial infarction in the 1 to 5 day post exacerbation period was not chosen a priori as the exposure for the main analysis.

Nevertheless, both reports are consistent with previous findings that acute lower respiratory tract infection and acute exposure to air pollution transiently increase the risk of myocardial infarction (Meier et al. 1998; Forastiere et al. 2005).

Moreover, the association between exacerbation of COPD and myocardial infarction is biologically plausible. The pathological features of exacerbation of COPD described in Section 1.5.1 such as increased systemic inflammation, tachycardia and hypoxia might be expected to favour plaque rupture and thrombus formation. Moreover, raised CRP, Il-6, fibrinogen and increased platelet activation have been reported in exacerbations of COPD, compared to the stable state, (Wedzicha et al. 2000; Hurst et al. 2006; Maclay, McAllister, Mills, Newby, et al. 2009) and inflammation is implicated in plaque rupture and thrombus formation (Libby 2002).

It is not known whether there is clinical consensus regarding the diagnosis of acute coronary syndrome in patients with exacerbation with COPD, nor is the prevalence of acute coronary syndrome in patients with exacerbation of COPD known.

1.6. FEV_1 as a prognostic marker

Notwithstanding causation, FEV_1 is of interest as a prognostic marker. FEV_1 has been found to predict a range of adverse events in addition to cardiovascular risk, including cancer from all causes, non-respiratory cancer, rupture of aortic aneurysm, and psychiatric illness (Pembroke et al. 2006; Hole et al. 1996; Brown & Powell 1999).

Several prognostic indices have been developed to help patients and clinicians decide whether cardiac surgery is appropriate. The European System for Cardiac Operative Risk Evaluation (EuroSCORE) is a widely used risk prediction tool that comprises seventeen clinical features (Nashef et al. 1999), and has good discrimination for early and late post-operative mortality (Nilsson et al. 2006).

However, because of an ageing population and changes in surgical practice over the last decade these clinical tools need to be updated (Nashef 2009), and since FEV_1 is a robust measure of respiratory physiology, and a strong predictor of adverse outcomes in a range of settings, it should be evaluated for inclusion in new risk prediction tools.

1.7. Summary and aims

Therefore, cardiovascular morbidity and mortality are common in COPD, having been diagnosed with COPD is associated with increased cardiovascular risk, and FEV_1 independently predicts cardiovascular morbidity and mortality.

Systemic vascular pathology has been proposed as a mechanism linking FEV_1 and COPD to cardiovascular morbidity and mortality, through various processes including systemic inflammation, endothelial dysfunction and susceptibility to connective tissue degradation.

Previous studies have identified that patients with COPD may be at increased risk of acute myocardial infarction during acute exacerbations, perhaps through pathophysiological changes such as hypoxia, tachycardia, and increased systemic inflammation.

Notwithstanding causation, the strong associations between FEV_1 and a variety of adverse outcomes mean that it may be a useful prognostic marker in patients undergoing cardiac surgery.

1.7.1. Hypotheses

Therefore, this thesis will address the following hypotheses:-

1 FEV_1 is a potentially useful prognostic marker in patients undergoing cardiac surgery.

2 Exacerbation of COPD partly accounts for the association between cardiovascular morbidity and mortality and COPD/airflow limitation, and acute coronary syndrome is common in exacerbation of COPD.

3 Pathological changes in the systemic vasculature partly mediate the association between COPD/ reduced FEV_1 and cardiovascular morbidity and mortality.

1.7.2. Aims

To address these broad hypotheses, this thesis has the following aims:-

- To test the hypothesis that FEV_1 predicts length of hospital stay and in-hospital mortality in patients undergoing cardiac surgery. Chapter 2.
- To identify whether there is a clinical consensus amongst Scottish Respiratory Consultants regarding the investigation of patients for acute coronary syndrome following admission to hospital with exacerbation of COPD. Chapter 3.
- To identify the prevalence of acute coronary syndrome in patients admitted to hospital with exacerbations of COPD in a prospective case-series. Chapter 4.
- To test the hypothesis that the extent of arterial stiffness is associated with the severity of emphysema in patients with COPD. Chapter 5.
- To test the hypothesis that arterial stiffness in the proximal aorta, measured via reduced distensibility of the ascending aorta on magnetic resonance (MR), is associated with severity of emphysema and reduced FEV_1 in a large population-based cohort, including participants with airflow limitation. Chapter 6.
- To test the hypothesis that decrements in the FEV_1 and increments in percent emphysema on computed tomography (CT) scans are associated with calcification of the vasculature from the ascending aorta to the iliac arteries. Chapter 7.

2. Analysis of routine data: FEV_1 predicts higher mortality and prolonged length of stay in patients undergoing cardiac surgery

2.1. Introduction

For more than 40 years cardiac surgery has been performed to relieve symptoms and improve outcomes in patients with coronary artery and valvular heart disease (Eagle et al. 2004). Whilst improvements in surgical technique have resulted in progressive reductions in operative morbidity and mortality, the aging population and increasing use of percutaneous treatments have resulted in older patients with more co-morbidity being referred for cardiac surgery (Peterson 2009).

Several prognostic indices have been developed to help patients and clinicians decide whether cardiac surgery is appropriate. The European System for Cardiac Operative Risk Evaluation (EuroSCORE) is a widely used risk prediction tool that comprises seventeen clinical features (Nashef et al. 1999), and has good discrimination for early and late post-operative mortality (Nilsson et al. 2006). It is recognised that changes in surgical practice over the last decade require these clinical tools to be updated (Nashef 2009). With increasingly elderly patients being considered for surgical management, markers which reflect general physiological reserve and severity of co-morbid disease may be particularly relevant to prognosis and should be evaluated for inclusion in new risk prediction tools.

FEV_1 is a robust accurate measure of pulmonary physiology, and is a strong predictor of mortality from cardiovascular, respiratory and other causes, independent of age, gender, race/ethnicity, socioeconomic status, blood pressure, diabetes and cholesterol (Hole et al. 1996; Friedman et al. 1976). However, studies directly examining whether FEV_1 predicts outcomes in cardiac surgery have been limited to small numbers of patients with chronic pulmonary disease (Fuster et al. 2006; Lizak et al. 2009). As such, the relationship between FEV_1 and clinical outcomes following cardiac surgery has not been established.

Therefore, the aim of this chapter is to test the hypothesis that FEV_1 predicts hospital stay and in-hospital mortality, and that this association is independent of having a

clinical history of pulmonary disease and other potential confounders including age, sex, smoking and socioeconomic status.

2.2. Methods

2.2.1. Study population

In a retrospective cohort study all patients aged 40 years or older who underwent coronary artery bypass grafting (CABG) and/or valve repair or replacement surgery from January 1st 2001 to December 31st 2007 at the Royal Infirmary of Edinburgh, Scotland, United Kingdom were identified. Patients who were not resident in the hospital catchment area or who underwent cardiac surgery as an emergency were excluded a priori on the basis that spirometry would not have been performed locally or would not have been feasible prior to surgery. Where patients had more than one operation during the study period, only the first operation was included.

2.2.2. Clinical characteristics and outcomes

Patient characteristics and details of their cardiac surgery, including length of hospital stay and in-hospital mortality, were obtained from medical records and recorded in an electronic cardiac surgical database (TOMCAT Clinical Systems, Philips Healthcare, Amsterdam, The Netherlands) by trained staff at the time of admission. This database is maintained to nationally agreed standards, which includes auditing of randomly sampled medical records and publication of statistics on missing data (Society for Cardiothoracic Surgery in Great Britain and Ireland 2008). In an external Scottish Quality Improvement Programme audit in 2008 these data were found to be 98.5% accurate.

An estimate of predicted operative mortality was derived using the EuroSCORE (Nashef et al. 1999). The EuroSCORE defines ‘chronic pulmonary disease’ as the long term use of bronchodilators or steroids for lung disease. In addition to ‘chronic pulmonary disease’, patient or clinician reported diagnoses of chronic obstructive pulmonary disease (COPD) and asthma were also recorded. The 2006 Scottish Index of Multiple Deprivation (SIMD) score was obtained from the recorded postal code and patients were stratified based on the national distribution of the SIMD in order to

provide an area-based measure of socio-economic status (Scottish Government 2005).

2.2.3. Spirometry

Height and weight were measured, and spirometry was performed, without the administration of a bronchodilator, on a wedge bellows spirometer to Association for Respiratory Technology and Physiology/British Thoracic Society standards (Model S, Vitalograph, Buckinghamshire, UK) by trained clinical physiologists in one of two lung function laboratories in Edinburgh. FEV_1 percent predicted was calculated using the European Coal and Steel reference equations (Quanjer et al. 1993). Airflow limitation was defined a priori as an FEV_1/FVC ratio below 0.7 and FEV_1 percent predicted less than 80% (NICE 2004). A broader definition of airflow limitation for use in sensitivity analyses included all patients with an FEV_1/FVC ratio below 0.7 regardless of the FEV_1 percent predicted.

2.2.4. Record linkage

Records from the cardiac surgery database were linked to the spirometry database for the same period. Within a secure health service environment date of birth, first name and surname were used to link records using Microsoft Access 2000. Personal identifiers and dates were removed following linkage and the irreversibly anonymised database was used for analysis. Where patients had spirometry performed more than once prior to surgery, the measure closest to the date of the operation was selected. Patient selection and matching were completed prior to all analyses.

2.2.5. Statistical analysis

For descriptive purposes, characteristics were compared for patients with and without spirometry records and by quintile of FEV_1 percent predicted, which is widely used in clinical practice. However, use of the current European prediction equations has been criticised on the grounds that they are not contemporary and were not obtained from original data (Degens & Merget 2008). As such all formal analyses were performed using FEV_1 with adjustment for age, sex, height and other covariates as appropriate. Proportional change in length of stay, and the odds ratio for in-hospital mortality were estimated by quintile of FEV_1, and per one standard deviation

decrement in FEV_1, using linear regression (log-transformed) and logistic regression respectively.

Discrimination of the existing EuroSCORE model was compared to a model including EuroSCORE and FEV_1 using the area under the curve (DeLong et al. 1988), and the more sensitive net reclassification and integrated discrimination indices (NRI and IDI respectively) (Pencina et al. 2008). The NRI compares models with and without a new marker of interest to estimate the proportion of patients more appropriately classified minus the proportion less appropriately classified under the new model. The IDI is a global measure of sensitivity weighted by specificity that is more sensitive than the area under the curve. Model calibration was compared using the le Cessie-van Houwelingen normal test statistic for the unweighted sum of squared errors (Hosmer et al. 1997).

In sensitivity analyses regression modelling was repeated following stratification by gender, smoking status, type and urgency of operation, and following exclusion of patients with a clinical history of asthma, COPD and 'chronic pulmonary disease' or airflow limitation on spirometry. Generalised additive models were used to explore non-linearity. Where data were missing, multiple imputation was used as the main approach with listwise deletion sensitivity analyses. Analyses were performed in SAS 9.2 (Cary, North Carolina, USA) and R version 2.9.2 (R Foundation for Statistical Computing, Vienna, Austria).

2.3. Results

Records meeting matching criteria were available for 2,082 patients (93%) of the 2,241 patients from the regional cardiac surgery database who met the eligibility criteria. The 159 patients without spirometry were more likely to have required urgent surgery (70 versus 54%, $p<0.001$), undergone previous surgery, and have a clinical history of COPD (3.8 versus 1.3%, $p=0.02$), but were otherwise similar to the 2,082 with matching records (Table 2-1). There were observed differences, of doubtful significance, in body mass index and prevalence of renal disease.

Table 2-1 Characteristics of patients with and without spirometry measures

	Spirometry	No spirometry	p-value
n	2082	159	
Age, years	67 (10)	68 (9)	0.07
Gender, male	1451 (69.7%)	115 (72.3%)	0.49
Deprivation (SIMD)			
First quintile	245 (11.8%)	16 (10.1%)	
Second quintile	447 (21.5%)	36 (22.6%)	
Third quintile	310 (14.9%)	26 (16.4%)	0.79
Fourth quintile	423 (20.3%)	28 (17.6%)	
Fifth quintile	657 (31.6%)	53 (33.3%)	
Type of Operation			
CABG	1330 (63.9%)	94 (59.1%)	
CABG and Valve	262 (12.6%)	26 (16.4%)	0.33
Valve	490 (23.5%)	39 (24.5%)	
Urgency of Procedure			
Elective	959 (46.1%)	47 (29.6%)	<0.001
Urgent	1123 (53.9%)	112 (70.4%)	
Previous cardiac surgery *	112 (5.4%)	16 (10.1%)	0.02
Height, cm	167 (9)	167 (9)	0.35
Weight, kg	78.7 (15.6)	77.1 (16.6)	0.20
Body Mass Index, kg/m^2	28.0 (4.7)	27.0 (4.8)	0.02

	Spirometry	No spirometry	p-value
n	2082	159	
Smoking Status			
Never Smoked	689 (33.4%)	55 (35.5%)	
Ex-Smoker	1071 (51.9%)	77 (49.7%)	0.85
Current Smoker	303 (14.7%)	23 (14.8%)	
Diabetes	351 (16.9%)	34 (21.4%)	0.15
Hypertension	1311 (63.6%)	93 (59.2%)	0.27
Renal Disease*	34 (1.6%)	9 (5.7%)	<0.003
Extracardiac Disease	199 (9.6%)	19 (11.9%)	0.33
Extracardiac Disease	199 (9.6%)	19 (12%)	
Previous Stroke or TIA	217 (10.4%)	18 (11.3%)	0.75
Recent Myocardial Infarction	1248 (60%)	103 (64.8%)	0.23
Atrial Fibrillation	181 (15.3%)	17 (20.7%)	0.15
Angina			
CCS0	527 (25.8%)	41 (27.0%)	
CCS1	207 (10.1%)	12 (7.9%)	
CCS2	417 (20.4%)	23 (15.1%)	0.25
CCS3	544 (26.6%)	38 (25.0%)	
CCS4	349 (17.1%)	38 (25.0%)	

	Spirometry	No spirometry	p-value
n	2082	159	
Dyspnoea			
NYHA 1	466 (22.9%)	39 (26.2%)	
NYHA 2	578 (28.4%)	30 (20.1%)	
NYHA 3	775 (38.1%)	47 (31.5%)	0.10
NYHA 4	216 (10.6%)	33 (22.1%)	
Left Mainstem Disease			
Present	474 (22.8%)	41 (25.8%)	0.67
Absent	1557 (74.8%)	114 (71.7%)	
Not Investigated	51 (2.5%)	4 (2.5%)	
Vessels >50% stenosis			
None	486 (24.2%)	35 (22.7%)	
One	163 (8.1%)	13 (8.4%)	0.94
Two	346 (17.3%)	25 (16%)	
Three	1010 (50%)	81 (52.6%)	
Left ventricular ejection fraction			
Normal	442 (23.2%)	37 (26.2%)	
Moderately impaired	1336 (70.2%)	86 (61.0%)	0.01
Severely impaired	126 (6.6%)	18 (12.8%)	
Chronic Pulmonary Disease*	10 (0.96%)	3 (1.89%)	0.26
COPD*	28 (1.3%)	6 (3.8%)	0.02
Asthma*	24 (1.3%)	2 (1.26%)	0.91

Mean (standard deviation) except where count (%). T-test for continuous measures and Chi-squared test for counts, except * where Fisher's exact test was used.

In patients with spirometry performed the mean (SD) age was 67 (10) years and 1,451 (70%) were male (Table 2). Spirometry was performed in the same year as surgery in 90% of patients, and in the same or previous year in 97%. Most patients had a history of cigarette smoking with 52% ex-smokers and 15% current smokers, but a clinical diagnosis of COPD was only recorded in 28 (1.3%), asthma in 24 (1.2%) and 'chronic pulmonary disease' in 20 (1.0%) patients. Airflow limitation identified on spirometry (FEV_1/FVC <0.7 and FEV_1 <80% predicted) was present in 318 (15%) patients.

Socioeconomic deprivation, urgent surgery, valve procedures, current smoking, diabetes mellitus, stroke, extra-cardiac arteriopathy (defined in the euroSCORE code as a history of claudication, documented carotid artery occlusion or >50% stenosis, or surgery for disease of the abdominal aorta, peripheral vasculature or carotid arteries), left ventricular impairment, pulmonary hypertension, atrial fibrillation and dyspnoea were more frequent in quintiles with lower FEV_1 percent predicted than those in higher quintiles, but the proportion of patients with a >70% stenosis in one or more of the main coronary arteries was similar across FEV_1 percent predicted quintiles (Table 2-2).

Table 2-2 Patient characteristics by quintile of FEV_1 percent predicted

	Q1	Q2	Q3	Q4	Q5
FEV_1 percent predicted, mean (range)	60 (20-75)	82 (75-88)	93 (88-98)	102 (98-108)	120 (109-177)
n	416	417	416	417	416
Age, years (mean (SD))	69 (9)	66 (10)	66 (10)	66 (10)	68 (10)
Gender, male	68.3	70.0	71.4	72.4	66.4
Deprivation (SIMD)					
First quintile (most)	18	12	9	14	8
Second quintile	24	21	24	22	17
Third quintile	14	17	18	12	15
Fourth quintile	18	23	20	18	22
Fifth quintile (least)	27	28	30	25	39
Height, cm – mean (SD)	168 (9)	168 (9)	168 (9)	168 (9)	166 (10)
Body mass index, kg/m^2 (mean (SD))	27.1 (4.9)	28.7 (4.7)	28.1 (4.4)	28.0 (4.6)	27.6 (4.3)
Smoking status					
Never smoked	23	28	34	37	45
Ex-smoker	59	53	50	50	48
Current smoker	19	19	16	13	7
Previous cardiac surgery	8.4	7.9	5.5	2.6	2.4
Diabetes	19	18	17	16	13
Hypertension	59	66	64	63	67
Renal disease	5	1	1	1	1

	Q1	Q2	Q3	Q4	Q5
FEV_1 percent predicted, mean (range)	60 (20-75)	82 (75-88)	93 (88-98)	102 (98-108)	120 (109-177)
n	416	417	416	417	416
Previous stroke or TIA	15	9	11	11	6
Extracardiac arteriopathy	11	12	10	8	6
Recent myocardial infarction	63	60	58	60	57
Atrial fibrillation	27	17	13	14	6
Vessels >70% stenosis					
None	31	23	22	23	21
One	8	9	7	6	10
Two	16	17	16	19	18
Three	44	51	54	52	51
Left ventricular ejection fraction					
Normal	61	69	72	72	78
Moderately impaired	28	22	24	25	17
Severely impaired	11	9	5	3	5
Pulmonary hypertension	30	27	20	6	11
Type of operation					
CABG	53.6	63.1	67.6	67.9	67.3
CABG and valve	14.2	13.0	12.3	10.3	13.2
Valve	32.2	24.0	20.2	21.8	19.5
Urgent surgery	59.6	52.0	55.3	52.3	50.5

Values are percentages unless stated

2.3.1. Length of stay

Median hospital stay was 3 days longer amongst patients in the lowest quintile for FEV_1 compared to patients in the highest quintile (1.53-fold longer; 95% CI 1.41-1.67; $p<0.001$), and this association persisted after adjusting for age, sex, height, weight, type of operation, urgency of procedure, deprivation score, smoking status, recent myocardial infarction, extracardiac arteriopathy, diabetes, hypertension, stroke, atrial fibrillation, left ventricular function, asthma, COPD, bronchodilator use, preoperative renal failure, and pre-operative angina and dyspnoea (1.35-fold longer; 95% CI 1.20-1.52; $p<0.001$) (Table 2-3).

Table 2-3 Length of stay by quintile of FEV_1

	Q1	Q2	Q3	Q4	Q5	SD decrement in FEV_1	p-value
FEV_1 litres, mean (range)	1.31 (0.35-1.70)	1.95 (1.71-2.20)	2.41 (2.21-2.62)	2.89 (2.63-3.15)	3.57 (3.16-5.80)	(800 ml)	
n	416	417	416	417	416		
LOS in days, median (IQR)	10 (7-15)	8 (7-13)	7 (6-10)	7 (6-9)	7 (6-8)		
Relative LOS unadjusted	1.53	1.40	1.25	1.10	1	1.17	<0.001
(95% CI)	(1.41-1.67)	(1.29-1.52)	(1.15-1.36)	(1.01-1.20)		1.14-1.20	
Relative LOS - model 1	1.53	1.38	1.21	1.07	1	1.17	<0.001
(95% CI)	(1.36-1.71)	(1.25-1.53)	(1.11-1.33)	(0.98-1.16)		1.12-1.21	
Relative LOS - model 2	1.35	1.30	1.16	1.05	1	1.12	<0.001
(95% CI)	(1.20-1.52)	(1.17-1.44)	(1.05-1.27)	(0.96-1.14)		1.07-1.17	

Relative LOS – proportional change in length of stay relative to reference category

Model 1 - adjusted for age, sex, height and body mass index

Model 2 – as model 2 additionally adjusting for type of operation, urgency of procedure, deprivation score, smoking status, recent myocardial infarction, extracardiac arteriopathy, diabetes, hypertension, stroke, atrial fibrillation, left ventricular function, asthma, COPD, chronic pulmonary disease, preoperative renal failure, pre-operative angina, pre-operative dyspnoea.

2.3.2. Mortality

Strong associations were found for in-hospital mortality and FEV_1 (Table 2-4). The unadjusted odds ratio (OR) for in-hospital death was 2.58-fold higher (95% CI 1.95-3.41; $p<0.001$) per standard deviation decrement in FEV_1 (800 ml). FEV_1 remained a strong predictor after adjusting for type of operation, smoking status, asthma, COPD, bronchodilator use, pre-operative angina and pre-operative dyspnoea (OR 2.11; 95%CI 1.45-3.08; $p<0.001$, Table 2-4).

Table 2-4 In-hospital mortality by quintile of FEV_1

	Q1	Q2	Q3	Q4	Q5	SD decrement in FEV_1 (800 ml)	p-value
FEV_1 litres, mean (range)	1.31 (0.35-1.70)	1.95 (1.71-2.20)	2.41 (2.21-2.62)	2.89 (2.63-3.15)	3.57 (3.16-5.80)		
n	416	417	416	417	416		
Mortality, n (%)	36 (8.7%)	16 (3.8%)	12 (2.9%)	3 (0.7%)	4 (1.0%)		
Odds Ratio unadjusted	9.76	4.11	3.06	0.75	1	2.58	<0.001
(95% CI)	(3.44-27.7)	(1.36 12.41)	(0.98-9.57)	(0.17-3.36)		1.95-3.41	
Odds Ratio - model 1	8.61	3.73	2.94	0.74	1	2.53	<0.001
(95% CI)	(2.58-28.81)	(1.13-12.33)	(0.91-9.53)	(0.16-3.36)		1.78-3.60	
Odds Ratio - model 2	5.23	2.76	2.28	0.69	1	2.11	<0.001
(95% CI)	(1.48-18.41)	(0.81-9.36)	(0.69-7.53)	(0.15-3.15)		1.45-3.08	

Model 1 - adjusted for age, sex, height and body mass index

Model 2 - as model 1 additionally adjusting for type of operation, smoking status, COPD, chronic pulmonary disease, pre-operative angina, pre-operative dyspnoea.

2.3.3. Airflow limitation on spirometry and FEV_1

Adjusting for the same covariates as in the main analyses, FEV_1 continued to predict hospital stay (800ml decrement in FEV_1; 1.26-fold longer; 95% CI 1.08-1.48, $p<0.001$), and mortality (800ml decrement in FEV_1; 2.28 OR; 95% CI; 1.19-4.41; $p=0.01$) after excluding individuals with airflow limitation on spirometry. Similar results were obtained when a broader definition of airflow limitation was used (FEV_1/FVC ratio <0.70, regardless of FEV_1 percent predicted, $p<0.001$, and $p=0.01$ respectively). The associations between FEV_1, length of stay and mortality appeared to be broadly linear (Figure 2-1), with no formal evidence for departure from linearity for either outcome ($p=0.13$, and $p=0.28$ respectively). Nor is there evidence of departure from linearity graphically, at least until the FEV_1 is over 4 litres, after which the data are relatively sparse.

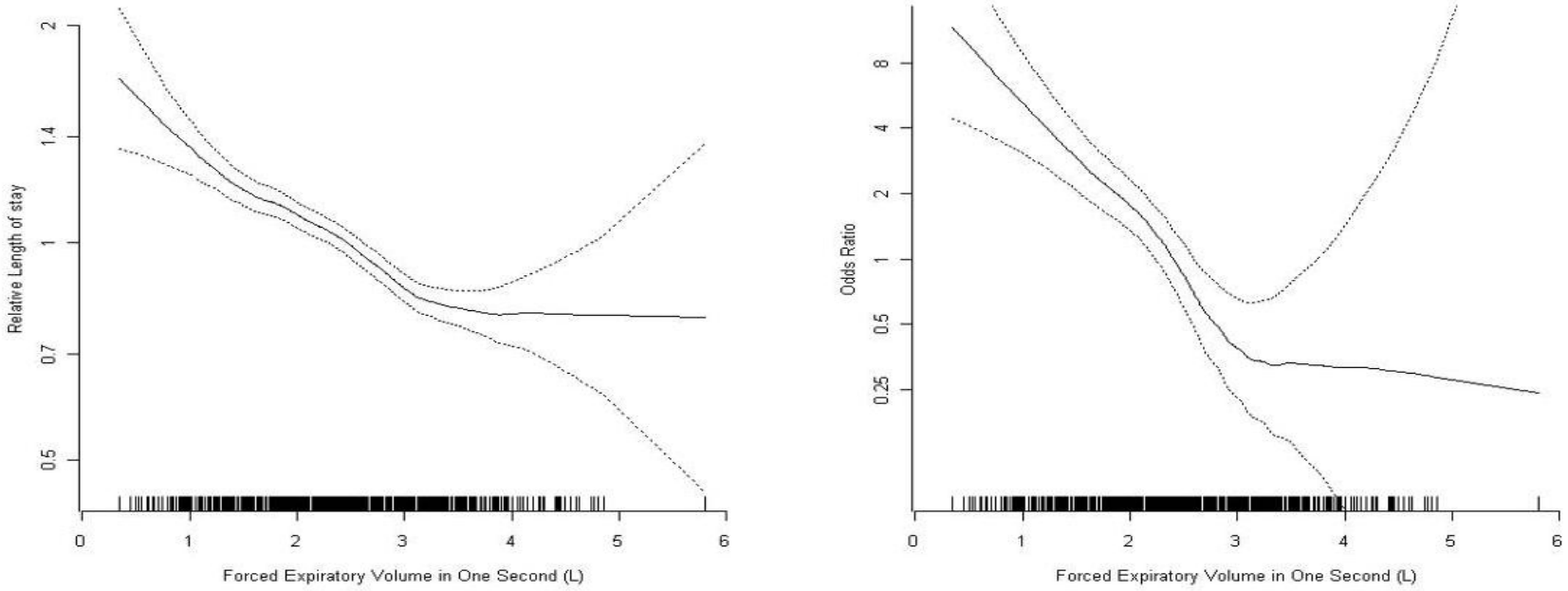

Figure 2-1 Association between FEV_1 and length of stay and mortality

a) Relative length of stay for a given FEV_1 compared to the length of stay for the mean FEV_1. b) Odds ratio for in-hospital mortality for a given FEV_1 compared to the odds ratio for the mean FEV_1. Estimates were obtained from generalized additive models using a loess smoothing function . A rug plot illustrates the density of the data for given value of FEV_1. Significance tests for non-linearity were p=0.11 and p=0.28 respectively.

2.3.4. FEV_1 compared to the EuroSCORE

FEV_1 remained strongly associated with mortality after adjusting for the EuroSCORE (OR 1.69; 95% CI 1.23-2.31, likelihood ratio statistic 11, 1 df, p <0.001). The area under the receiver operator characteristic curve (AUC) was higher for EuroSCORE than FEV_1, but the difference was not statistically significant (AUC 0.78 and 0.74 respectively, p=0.15, Figure 2-2). Similarly, the addition of FEV_1 to the EuroSCORE increased the AUC when compared to the EuroSCORE alone (AUC of 0.80 and 0.78 respectively), but the difference was not statistically significant (p=0.26).

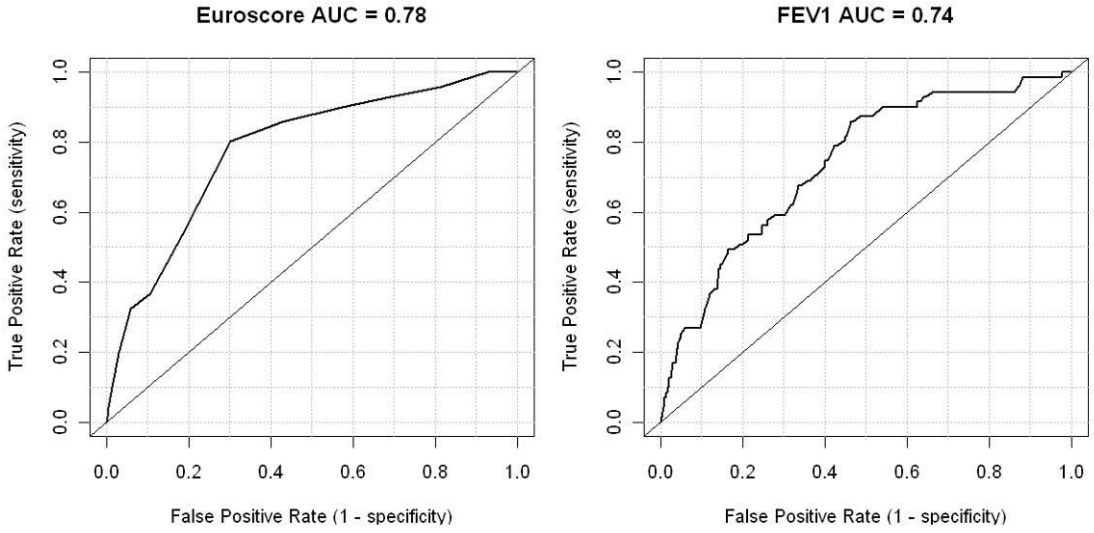

Figure 2-2 Areas under the receiver operator curve for EuroSCORE and for FEV_1

However, using a more sensitive measure of discrimination, the Net Reclassification Index (Pencina et al. 2008), 27% of patients (95% CI 4 to 51%, p <0.001) were more appropriately classified with the EuroSCORE alone than with FEV_1 alone, while 36% of patients (95% CI 12-59%; p=0.003) were more appropriately classified when FEV_1 was combined with the EuroSCORE compared to the EuroSCORE alone. The Integrated Discrimination Index yielded similar results for each of these comparisons: EuroSCORE alone versus FEV_1 alone (IDI 0.02; 95% CI 0.00 to 0.03; p=0.01) and EuroSCORE alone versus FEV_1 in combination with EuroSCORE

(IDI=0.01; 95% CI 0.00 to 0.02; p=0.006). Model calibration was also better with FEV_1 and EuroSCORE combined (z=0.14; p=0.89) than with the EuroSCORE alone (z =1.27, p=0.21).

2.3.5. Sensitivity analyses

Similar associations were found for length of stay and mortality after stratifying by operation type and urgency, gender and smoking status. Results obtained using listwise deletion were similar to those obtained using multiple imputation.

2.4. Discussion

FEV_1 is a strong predictor of longer hospital stay and in-hospital mortality following elective and urgent cardiac surgery. These associations persist after adjusting for multiple covariates including a clinical diagnosis of COPD, and airflow limitation on spirometry. Addition of FEV_1 to the current and most widely used peri-operative risk prediction model, the EuroSCORE, improved discrimination and calibration for in-hospital mortality.

COPD is the commonest cause of reduced FEV_1 in adults (Bednarek et al. 2008), and is an established risk factor for in-hospital and long-term mortality following cardiac surgery (Clough et al., for the Northern New England Cardiovascular Disease Study Group 2002; Rosenthal et al. 2003; Leavitt et al., for the Northern New England Cardiovascular Disease Study Group 2006). Two recent studies confirm that FEV_1 is associated with poorer outcome in patients with chronic lung disease undergoing cardiac surgery, however due to the small number of patients with measured FEV_1 (n<150), linearity was not assessed and adjustment for potential confounders was limited (Fuster et al. 2006; Lizak et al. 2009). In the current study there was a near linear relationship between FEV_1 and both hospital stay and in-hospital mortality across the spectrum of lung function, and this association persisted after controlling for other potentially important confounders including age, sex, cardiovascular risk factors and socioeconomic status.

The prevalence of airflow limitation on spirometry was much higher than that recorded in the clinical database, and at 15% overall was closer to the 11.8% prevalence for men and 8.5% prevalence for women estimated in a large

international cross-sectional study in individuals aged 40 and over (Buist et al. 2007). As such, the routine inclusion of FEV_1 and FVC in cardiac datasets may improve clinical detection of COPD. Nevertheless, higher FEV_1 continued to predict lower hospital stay and mortality even after excluding any patient with evidence of airflow limitation on spirometry, suggesting that higher FEV_1 may is a potentially useful marker even amongst people with normal lung function.

However, to justify inclusion in risk prediction tools, putative markers should also improve discrimination (distinguishing patients with and without adverse events) and/or calibration (precision of estimates of risk of adverse events) (Cook 2007). In a recent review of nineteen published risk prediction models the EuroSCORE was found to be the best discriminator for 30-day and one year mortality after cardiac surgery (Nilsson et al. 2006). When combined with EuroSCORE FEV_1 improved discrimination compared to EuroSCORE alone. The area under the curve was higher, although the difference was not statistically significant, while the more powerful Net Reclassification Index was highly statistically significant, and estimated that over a third of patients would be assigned a more appropriate risk of in hospital death when FEV_1 was combined with the EuroSCORE compared to the EuroSCORE alone. Calibration was also improved on adding FEV_1 to the EuroSCORE. These findings are from a single centre and should be validated in an independent dataset including a range of surgical practices. Nevertheless, FEV_1 appears to have additional value, beyond identifying patients with chronic lung disease, as an independent predictor of outcome in patients undergoing cardiac surgery.

Moreover, FEV_1 is not a costly new biomarker, but rather a widely available physiological measurement that is already performed in over 90% of patients undergoing elective and urgent cardiac surgery. FEV_1 remains stable over time and can therefore be measured at an early stage of evaluation prior to cardiac surgery (Anthonisen et al. 1994). In many healthcare settings it may be possible to link spirometry and cardiac surgery records deterministically, using unique hospital numbers, at minimal cost to facilitate the development and validation of a clinical risk score that incorporates FEV_1. Therefore, FEV_1 is an attractive candidate for inclusion in prognostic models.

The mechanisms responsible for the inverse association between FEV_1 and adverse outcomes are unknown, and have not been addressed in this study. Reductions in FEV_1 may reflect both increased exposure and susceptibility to pro-inflammatory factors, such as cigarette smoking, environmental pollution and microbial infection, or may simply be an indicator of the patients' capacity to withstand the insult of major surgery, reflecting their respiratory reserve, nutritional status or muscle strength. If the latter, then FEV_1 may be capturing similar information to that obtained in the recent study by Lee et al in which questionnaire-based measures of frailty were found to be related to both in-hospital mortality and mid-term survival (Lee et al. 2010).

2.4.1. Limitations

The spirometry database was linked to the regional cardiac surgery database using non-unique shared fields, rather than a single unique identifier such as a hospital number. Under the agreed linkage procedures, permission was not obtained to allow access to medical records and so the sensitivity and specificity of the linkages could not be assessed, and it is possible that a few records pertaining to different individuals have been inadvertently linked. However, any such mismatches would be likely to result in non-differential misclassification bias, underestimating the strength of association between FEV_1 and both mortality and length of stay. All known prognostic markers were not recorded at the time of the matching and anonymisation, and therefore active endocarditis, critical pre-operative state, or post-infarct septal rupture were not included in the EuroSCORE calculation. However, these clinical variables are present in less that 0.1% of patients undergoing urgent cardiac surgery in this regional centre (results not shown) and similar associations for FEV_1 and length of stay and mortality were found even when restricting the analysis to elective surgery, making confounding by these 'critical illness' variables unlikely.

FEV_1 was analysed as a continuous variable and cut-offs were not chosen in a data-drive manner, but the discrimination and calibration for FEV_1 are likely to be slight overestimates as these were evaluated using the same data with which the associations between FEV_1 and length of stay and in-hospital mortality were identified, and the findings should be confirmed in an independent dataset.

2.4.2. Conclusions

FEV_1 is a strong and independent predictor of length of stay and in-hospital mortality following elective and urgent cardiac surgery, and improves the discrimination of existing risk prediction tools. Spirometry is a widely available non-invasive physiological measure that is already performed in of the majority of patients undergoing cardiac surgery. FEV_1 should be included in prospective studies of surgical outcome, and be formally evaluated for inclusion in new cardiac surgery risk prediction tools.

In the remaining chapters different mechanisms/processes linking COPD/reduced FEV_1 and cardiovascular risk are addressed. In Chapters 3 and 4 the role of exacerbation of COPD is examined, and in Chapters 5, 6, and 7 the relationship between COPD, reduced FEV_1 and emphysema and the systemic vasculature are examined.

3. Survey of respiratory consultants in Scotland: Opinions on the investigation of acute cardiac events following admission to hospital with acute exacerbations of chronic obstructive pulmonary disease

3.1. Introduction

Cardiovascular diseases is common in COPD (Section 1.2.1) and the risk of acute myocardial infarction appears to be yet higher in the period during and immediately following diagnosis with an acute exacerbation of chronic obstructive pulmonary disease (hereafter exacerbation) (Huiart et al. 2006; Donaldson et al. 2010).

Furthermore, coronary events may present without chest pain (Canto et al. 2000), are missed even in simple chest pain presentations (Collinson et al. 2000) and may be more likely to be missed in more complex presentations, such as when patients have other acute illnesses, such as exacerbation of COPD.

Although published guidelines emphasise 'extra-pulmonary manifestations' in COPD, they do not address whether and how patients with exacerbations should be investigated to identify acute cardiac disease (Gold Executive Committee 2008; American Thoracic Society/European Respiratory Society 2004; NICE 2004).

Therefore, the aim of this chapter is to identify whether there is clinical consensus amongst Scottish Respiratory Consultants regarding the investigation of patients for acute coronary syndrome following admission to hospital with exacerbation of COPD.

3.2. Methods

Seventy-two Scottish Respiratory Consultants were e-mailed a link to a web-based survey (Figure 3-1. The survey consisted of multiple choice and Likert Scale questions about the investigation of chest pain in exacerbations. Items included were obtained from the most comprehensive systematic review examining the value and limitations of the chest pain history and presence of risk factors in the identification of patients at increased risk of acute myocardial infarction (Swap & Nagurney 2005). Consultants who did not respond to the first invitation were sent a second email.

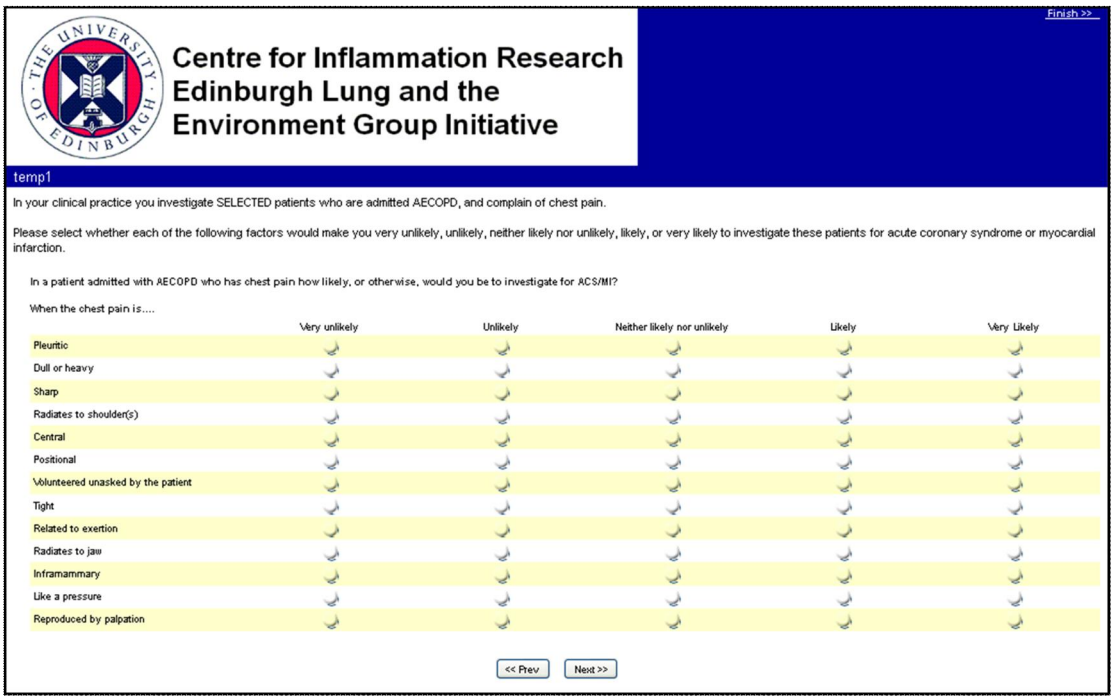

Figure 3-1 Example question from online questionnaire

3.3. Results

There were 46 (64%) respondents overall, and 33 (46%) answered additional questions about the usefulness of the available tests.

Two respondents screen all exacerbation patients for coronary events regardless of symptoms, 15 screen all those with chest pain, while 28 respondents (61%) investigate only selected exacerbation patients with chest pain.

In those who investigate selected patients, the most important determinant was the chest pain character. COPD and exacerbation characteristics were not important determinants (Table 3-1).

Table 3-1 Self-reported determinants in respondents who reported that they investigate selected patients with exacerbation who complain of chest pain

Determinant	Respondents, n (%)
Likely or very likely to investigate	
Radiates jaw	26 (100.0)
Exertional	22 (84.6)
Dull or heavy	22 (84.6)
Arrhythmia	21 (80.8)
Hypotensive (systolic <90)	18 (69.2)
Previous MI	18 (69.2)
Central	16 (61.5)
Pressure	16 (61.5)
Unlikely or very unlikely to investigate	
Pleuritic	24 (92.3)
Positional	22 (84.6)
Reproduced by palpation	16 (61.5)
Infective Exacerbation	10 (38.5)

Determinant	Respondents, n (%)
Neither likely nor unlikely to investigate	
Severe COPD (FEV_1<30)	19 (73.1)
Moderate COPD (FEV_1 30 to 50)	21 (80.8)
Mild COPD (FEV_1 >50)	19 (73.1)
Complains of breathlessness	18 (69.2)
Complains of wheeze	19 (73.1)
Complains of cough	18 (69.2)
Requires steroids for this exacerbation	17 (65.4)
Requires antibiotics for this exacerbation	17 (65.4)
Pyrexial (T>37.5)	16 (61.5)
Hypoxic (oxygen saturation <92%)	17 (65.4)

There was considerable heterogeneity amongst the 23 participants who answered the additional questions on the usefulness of serial ECG and troponin for confirming and excluding acute coronary syndrome in patients with acute exacerbation of COPD (Table 3-2).

Table 3-2 Perceived usefulness of serial electrocardiograms and serum troponin in patients with acute exacerbation of COPD

	Usefulness of ECG		Usefulness of troponin	
	To exclude	To confirm	To exclude	To confirm
Agree/Strongly Agree	13 (57)	17 (74)	18 (78)	14 (61)
Neither agree nor disagree	3 (13)	3 (13)	3 (13)	8 (35)
Disagree/Strongly Disagree	7 (30)	3 (13)	2 (9)	1 (4)

3.4. Discussion

The results of this survey suggest that approximately 60% of Scottish Respiratory Consultants investigate patients with exacerbations for the presence of myocardial infarction only when features of the chest pain history or the presence of cardiovascular risk factors suggest that there is an increased risk.

These results were obtained using self report and the true extent to which patients admitted to hospital with exacerbations are investigated for the presence of acute coronary syndrome with troponin samples and serial electrocardiograms is unknown.

However, these findings are likely to reflect the respondents' views on ideal practice, and this differs considerably from that outlined in the recent guidance from the National Institute for Clinical Excellence (NICE) for patients presenting with acute chest pain. The NICE guidance, based largely upon the results from three systematic reviews and one cohort study, suggests that although features of the chest pain history and the presence of established risk factors do predict acute coronary syndrome, they do so with poor precision, and that additional diagnostic testing is therefore needed when acute coronary syndrome is suspected (NICE 2010).

However, like acute coronary syndrome, exacerbation is itself a recognised cause of chest tightness and shortness of breath (Gold Executive Committee 2008), and raised troponin in the presence of normal coronary angiography has been described in patients with exacerbation (Mahajan et al. 2006). As such, patients with exacerbation

may be at risk of both under-diagnosis and over-diagnosis of acute coronary syndrome.

Fewer participants answered additional questions on the usefulness of ECGs and troponin in excluding or confirming acute coronary syndrome in the context of acute exacerbation of COPD. Nevertheless, there was considerable heterogeneity among those who did. This variability among responding clinicians may reflect the lack of studies examining serial ECG changes and raised troponin in the published literature.

3.4.1. Conclusion

There was no clear clinical consensus regarding the investigation of acute coronary syndrome in this survey, and patients with exacerbations are at theoretical risk of both under-diagnosis and over-diagnosis. As such, further research is justified to address this clinical problem. Since the prevalence of acute coronary syndrome in exacerbations is unknown, the prevalence of chest pain, serial electrocardiogram changes, and serum troponin were subsequently studied in a case-series of patients with exacerbations (Chapter 4).

4. Case series of patients with acute exacerbation of COPD: prevalence of chest pain, electrocardiogram changes, and raised troponin

4.1. Introduction

Coronary heart disease is a major cause of death in COPD (Section 1.2.1), both conditions share common risk factors, and reduced FEV_1, a characteristics feature of COPD, is an independent risk factor for cardiovascular morbidity and mortality (Section 1.2.3).

Evidence from healthcare utilisation data suggest that the risk of myocardial infarction may be further increased during exacerbations in patients with COPD (Huiart et al. 2006; Donaldson et al. 2010), while raised troponin has been found to be associated with increased mortality in exacerbation of COPD (Baillard et al. 2003; Brekke, Omland, Holmedal, et al. 2008). When troponin was measured in a consecutive sample of 71 patients with severe exacerbation of COPD, the in-hospital mortality was considerably higher when troponin was raised compared to when troponin was not raised, with 8 deaths (62% mortality) and 10 deaths (17% mortality) respectively (Baillard et al. 2003). Moreover, raised CRP, Il-6, fibrinogen and increased platelet activation have been reported in exacerbations of COPD, compared to the stable state, (Wedzicha et al. 2000; Hurst et al. 2006; Maclay, McAllister, Mills, Newby, et al. 2009) and inflammation is implicated in plaque rupture and thrombus formation. (Libby 2002).

One retrospective case-note review has examined the prevalence of raised troponin in patients admitted to hospital with exacerbation of COPD (Harvey & Hancox 2004) but no prospective study has systematically investigated patients admitted to hospital with exacerbations of COPD for evidence of acute coronary syndrome.

Therefore, the aim of this chapter is to identify the prevalence of acute coronary syndrome in patients admitted to hospital with exacerbations of COPD in a prospective a case-series.

4.2. Methods

Patients were recruited at 4 hospitals in Central Scotland, Edinburgh Royal Infirmary, The Royal Infirmary of Glasgow, Monklands District General Hospital and Crosshouse District General Hospital. At each site the local investigator recruited patients from accident and emergency and acute medical (admission) units. Patients aged 40 or older, diagnosed as having an acute exacerbation of COPD by a medical or respiratory consultant physician, and with a ten or more pack year history of cigarette smoking were recruited. Patients were excluded if the primary presenting complaint was chest pain, more than 48 hours had elapsed since admission, an alternative diagnosis was suggested by the admission chest x-ray, or pulmonary embolism was confirmed on computed tomography pulmonary angiography.

Acute coronary syndrome is defined as raised troponin in the presence of a consistent clinical history (Alpert et al. 2000). However, exacerbation of COPD might plausibly cause raised troponin independently of coronary disease (Mahajan et al. 2006). Therefore, a priori, acute coronary syndrome during acute exacerbation of COPD was defined as raised troponin, chest pain, and indicative serial electrocardiogram (ECG) changes.

A detailed chest pain and exacerbation history was completed, and recorded on a standard form (Figure 4-1). The details from the form were later entered onto an online form with validation at each centre. If an admission ECG had been performed then this was obtained. If not, an admission ECG was performed by the investigator, provided this could be done within 24 hours of admission. A second ECG was performed between 12 and 36 hours after the initial ECG. Where one or more ECG obtained prior to the admission was available a copy was obtained. A non-fasting blood sample was taken and each local hospital laboratory measured serum troponin, High Density Lipoprotein (HDL) and total cholesterol, triglycerides, full blood count, and CRP. Where patients reported chest pain, the sample was taken not less than 12 hours after the most recent episode, otherwise troponin was measured not less than 12 hours following admission. Spirometry results were either obtained from the patient's case notes, or from the local lung function service. Research Ethics Committee Approval was obtained and patient consent was obtained for all study protocols and procedures (06/MRE10/78).

ACS and AECOPD Form version 2.2 Created on 10/24/2006 11:42 AM

Symptoms of Current Exacerbation

Chest Pain Characteristics

Stable COPD Characteristics

Usual Drugs

Risk Factors for Coronary Heart Disease

Admission Observations

Arterial Blood Gases on Admission

CXR findings

Study Blood Results

Therapy During Exacerbation

ACS and AECOPD Form version 2.2 Created on 10/24/2006 11:42 AM

Figure 4-1 Data collection form

Toponin I (Abbott Architect, Illinois, USA) was measured in Edinburgh Royal Infirmary, The Royal Infirmary of Glasgow, and Troponin T (Roche, Basle, Switzerland) was measured in Monklands and Crosshouse District General Hospitals. The American College of Cardiology/European Society of Cardiology (ACC/ESC) joint guidelines for the definition of myocardial infarction recommend using the 99th percentile of the normal reference population to define raised troponin, and that the assay should achieve a co-efficient of variation of ≤ 10% (10% CV) at the 99th percentile value (Alpert et al. 2000). However, until recently, no troponin assay could achieve this level of precision, and therefore the recommendation of Apple et al to define the cut-off as the 10% CV level was followed, as was the recommendation to express the magnitude of elevation in troponin as multiples of the 10% CV level (Apple et al. 2002).

All ECGs were coded using the Minnesota Code (Prineas 1982). A single reader (David McAllister) coded all ECGs blinded to all clinical features, blood results and whether the ECG was the first or second ECG following admission, or an ECG obtained prior to admission. In 48 ECGs collected at the Glasgow site Minnesota codes were also identified electronically. Agreement for electronic and paper reads for the presence/absence of Q-waves, ST depression and T wave flattening/inversion was calculated (Kappa=0.73, 0.61 and 0.57 respectively). Serial ECG changes indicative of an acute cardiac event were defined using the Minnesota code criteria for independently read serial ECGs (Prineas 1982, p.204). All ECGs were additionally coded using the Cardiac Injury Infarction Score under the same conditions (Rautaharju et al. 1981).

Although the occurrence of acute coronary syndrome in the absence of chest pain is well documented (Canto et al. 2000), certain features of the chest pain history are recognised as being indicative of a higher risk of an ischaemic event (pain which is “like a pressure”, radiates to either shoulder or arm, or is related to exertion) while others are indicative of a reduced risk of an ischaemic event (pleuritic, related to movement, reproduced by palpation, sharp or of very short or long duration (<2 min or >12 hours) (Swap & Nagurney 2005). On this basis chest pain was categorised as high risk if only high risk features were present in the history, low risk if only low risk features were present in the history, both if a combination of both high and low

risk features were present, or indeterminate in neither high nor low risk features were present.

The prevalence of chest pain, raised troponin and serial ECG changes was calculated along with 95% confidence intervals, using the Score test for small samples where the prevalence was <0.10. In exploratory analyses, associations between patient characteristics and raised troponin were examined using Fisher's exact test, for which all associations where the p-value was <0.10 are reported. Analyses were performed using SAS version 9.2 (Cary, North Carolina, USA) and R version 2.9.2 (Vienna, Austria).

4.3. Results

A total of 242 patients were recruited, 143 from Edinburgh Royal Infirmary, 48 from the Royal Infirmary of Glasgow, 42 from Monklands District General Hospital and 9 from Crosshouse District General Hospital. The mean (SD) age was 69 (9), 108 (45%) were male and almost half were current smokers, with the majority having severe or very severe airflow limitation on spirometry (Table 4-1). All patients were breathless on admission, increased sputum volume was present in 130 (54%) and sputum purulence in 141 (58%), leukocytosis in 113 (47%) and raised CRP (>6 mg/dL) in 158 (74%). All were treated with nebulised bronchodilators, 217 (90%) with oral prednisolone, and 164 (68%) with antibiotics. The median (IQR) length of stay was 5 (3-8) days and 21 (15%) of the 143 patients at the Lothian site died within 12 months of admission.

Table 4-1 Patient characteristics

n	242
Stable characteristics	
Age, years, mean (SD)	69 (9)
Male Gender, n (%)	108 (45%)
Height, metres, mean (SD)	1.62 (0.10)
Current Smoker, n (%)	115 (48%)
Pack Years, median (IQR)	50 (33-63)
FEV_1, litres, median (IQR)	0.90 (0.68-1.20)
FVC, litres, median (IQR)	2.05 (1.63-2.65)
FEV_1/FVC ratio, median (IQR)	44 (35-55)
Severity of obstruction, median (IQR)	
Mild	10 (5%)
Moderate	59 (32%)
Severe	65 (35%)
Very severe	52 (28%)
Performance status ≥ 3, n (%)	73 (31%)
Long term oxygen therapy, n (%)	40 (17%)
Home Nebulisers, n (%)	119 (49%)
Long-acting beta agonists, n (%)	172 (71%)
Long-acting anticholinergics, n (%)	120 (50%)
Methylxanthines, n (%)	34 (14%)
Inhaled corticosteroid, n (%)	195 (81%)
Long term oral steroids, n (%)	6 (2%)

n	242
Exacerbation characteristics	
MRC Dyspnoea Score ≥ 4, n (%)	216 (92%)
Heart rate, mean (SD)	102 (20)
Respiratory Rate, mean (SD)	24 (5)
Systolic BP, mean (SD)	135 (25)
Diastolic BP, mean (SD)	73 (16)
Arterial blood gases, mean (SD)	
Hydrogen	41 (8)
PaO2	11 (4)
PaCO2	6 (2)
Anthonisen type, n (%)	
Type 1	110 (45%)
Type 2	51 (21%)
Type 3	67 (28%)
Leukocytosis (WCC >11)	113 (47%)
Raised CRP (>6 mg/dl), n (%)	158 (74%)
Haemoglobin, g/dl, mean (SD)	135 (18)
Prescribed antibiotics, n (%)	164 (68%)
Prescribed oral prednisolone, n (%)	217 (90%)
Treated with non-invasive ventilation	15 (6%)
Length of stay, median (IQR)	5 (3-8)
12 month mortality (Lothian), n (%)	21 (15%)

The patients were similar to those recruited in the 2008 British Thoracic Society Audit of patients admitted to hospital with acute exacerbation of COPD (Table 4-2).

Table 4-2 Comparison of patient characteristics for this case-series with those from the BTS COPD Audit 2008

	Case series	BTS Audit
Age, mean, years	69	73
Male sex, %	45%	50%
Length stay, median, days	5	5
Height, median, m	1.62	1.64
FEV_1 percent predicted, median	43%	38%
Current smoker, %	48%	33%
MRC 4-5 prior admission, %	65%	67%
Systemic steroids within 24h, %	90%	86%
Antibiotics within 24h, %	68%	81%
Acidotic on admission, %	21%	20%
Non-invasive ventilation, %	6%	11%
Sputum vol increased, %	54%	66%
Sputum purulence increased, %	58%	61%
Albumin g/dl, median	39	39
Creatinine, mmol/l, median	83	83
Ischaemic heart disease, %	32%	25%
Stroke, %	10%	6%
Diabetes, %	12%	12%

Cardiovascular risk factors were common (Table 4-3). Over 30% had a past medical history of ischaemic heart disease, 34 (14%) had previous stroke or peripheral vascular disease, with 101 (42%) having vascular disease at any site. Hypertension and hypercholesterolaemia were also common. Non-fasting HDL cholesterol and cholesterol:HDL ratio were 1.73 (0.61) mmol/l and 2.97 (1.07) respectively.

Amongst the 141 patients without known vascular disease 19 (13%) had an estimated (Framingham) risk of a cardiac event within 10 years of 20% or greater (Expert Panel on Detection, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) 2001). Around one third of patients were on regular statin therapy, and 96 (40%) were on antiplatelet therapy, although only 5 (2%) were on a beta-blocker.

Table 4-3 Cardiovascular risk factors and therapy

n	242
IHD, n (%)	
None	161 (69%)
Diagnosed by generalist	18 (8%)
Diagnosed by specialist	19 (9%)
Confirmed*	34 (15%)
Stroke or peripheral vascular disease, n (%)	34 (14%)
Hypertension, n (%)	90 (37%)
Hypercholesterolaemia, n (%)	76 (31%)
Diabetes, n (%)	30 (12%)
Family History of IHD, n (%)	76 (31%)
Creatinine >120 mmHg, n (%)	24 (10%)
Non-fasting lipids, mean (SD)	
HDL Cholesterol, mmol/l	1.73 (0.61)
Cholesterol:HDL Ratio	2.97 (1.07)
Triglycerides, mmol/l	1.45 (0.87)

n	242
Nitrate or nicorandil, n (%)	35 (14%)
Calcium channel blocker, n (%)	38 (16%)
Beta blocker, n (%)	5 (2%)
ACE-inhibitor/ AR2Blocker, n (%)	44 (18%)
Diuretic, n (%)	82 (34%)
Statin therapy, n (%)	85 (35%)
Antiplatelet therapy, n (%)	96 (40%)
Antidiabetic therapy, n (%)	13 (5%)

*Confirmed IHD refers to ischaemic heart disease confirmed through diagnostic exercise tolerance testing, angiography, or proven myocardial infarction.

Chest pain was also common, with 124 (51%; 95% CI 48 to 58%) patients reporting chest pain, which was most commonly tight or sharp, but was frequently related to exertion (Table 4-4).

Table 4-4 Chest pain

Characteristics	n (%)
Duration <2 min or >12 hours†	87 (82%)
Central	76 (61%)
Radiated to arm or jaw*	13 (11%)
Character	
Tight	60 (48%)
Sharp†	24 (19%)
Dull	12 (10%)
Like a pressure*	11 (9%)
Heavy	4 (3%)
Burning	1 (2%)
Gripping	2 (2%)
Autonomic symptoms (volunteered)	8 (6%)
Precipitating factors	
Exertion*	62 (52%)
Exertion, but pain also present at rest	44 (36%)
Deep inspiration†	7 (6%)
Coughing	20 (16%)
Palpation (pain reproduced) †	11 (9%)

Characteristics	n (%)
Relieving factors (partial or complete)	
Nitrate therapy	18 (15%)
Bronchodilator therapy	15 (12%)
Oxygen therapy	13 (10%)
Had similar pain previously	
During an exacerbation	67 (54%)
When stable	31 (25%)
Summary of chest pain	
High risk features only	50 (40%)
Low risk features only	21 (17%)
Low and high risk features	22 (18%)
Neither low nor high risk features	31 (25%)

† Chest pain features associated with low risk, *chest pain features associated with high risk

Sinus tachycardia was the commonest abnormality on admission ECG and was found in 112 (46%) patients. Fourteen (6%) patients had atrial fibrillation, 15 (6%) had right bundle branch block with 12 (5%) having left bundle branch block. Twenty (8%) had p-pulmonale. Diagnostic Q-waves and T-wave inversion were common (34 (14%) and 37 (15%) patients respectively), and the mean (SD) cardiac injury infarction score was 16 (10). Eighteen (7.5%) patients had no ECG within the first 24 hours of admission, while 21 (8.6%) had no second ECG. Only 3 patients developed Q-waves during admission, although serial changes in T-wave inversion/flattening and ST depression were common (65 (32%) and 19 (9%) respectively). Thirteen (6%) had serial changes in ST elevation (Table 4-5).

Table 4-5 Characteristics of first admission ECG and serial changes

Initial ECG	N	242
	Conduction defects	
	First degree block (63)	1 (0.4%)
	Incomplete RBBB (73)	10 (4%)
	Complete RBBB (721)	5 (2%)
	Incomplete LBBB (76)	8 (3%)
	Complete LBBB (711)	4 (2%)
	Arrhythmias	
	Sinus tachycardia (87)	112 (46%)
	Premature atrial/junctional beats (811,813)	17 (7%)
	Premature ventricular beats (812, 813)	6 (2%)
	Atrial fibrillation (831 or 833)	14 (6%)
	Wandering atrial pacemaker (814)	1 (0.4%)
	Other	
	p-pulmonale (93)	20 (8%)
	Low QRS amplitude (91)	3 (1%)
	Diagnostic Q waves (D1)	34 (14%)
	Equivocal Q waves (E1)	20 (8%)
	ST elevation with T-wave inversion (D2)	2 (0.8%)
	ST depression (E2)	32 (13%)
	T waves inverted or flat (E3)	58 (24%)
	ST elevation without T wave inversion (E4)	7 (3%)
	Cardiac Injury Infarction Score, mean (SD)	16 (10)

Serial change	N	203
	Major Q-waves	3 (1.5%)
	T-wave inversion/flattening	65 (32%)
	ST depression	19 (9%)
	ST elevation	13 (6%)
	Cardiac Injury Infarction Score, mean (SD)	-1 (9)

Twenty-four (10%) patients had elevated serum troponin, with 22 (9%) patients having a level greater than twice the cut-off and 15 (6%) having a serum troponin level greater than three times the cut-off. Of those with raised troponin, 11 had serial ECG changes (new Q waves or serial changes in T-waves or ST segments), and 13 had chest pain. Six patients had chest pain, ECG changes and raised troponin. As such, by the a priori definition, the prevalence of acute cardiac events was 2.5% (95% CI 1.0 to 5.6%, Table 4-6).

Table 4-6 Chest pain and ECG changes in each patient with raised troponin

	ECG Summary	Chest pain
	Troponin >1 x lower limit of detection	
-	Inverted T waves, no repeat ECG	None
-	No ischaemic features	Tight
	Troponin >2 x lower limit of detection	
-	Diagnostic Q waves and serial T wave changes	Central, lasting less than 2 minutes
-	Diagnostic Q waves and serial T wave changes	Tight, pleuritic
-	Serial ST elevation, without serial T wave changes	None
-	Serial T wave changes	None
-	Diagnostic Q waves	None
-	No ischaemic features	Central, tight, relieved by bronchodilators/oxygen
-	No ischaemic features	None

	ECG Summary	Chest pain
	Troponin >3 x lower limit of detection	
-	New diagnostic Q waves, and serial T wave changes	Central, sharp
-	Serial ST depression	Tight, lasting less than 2 min, exertional, radiating to arm/jaw
-	Serial ST depression	None
-	Diagnostic Q waves and serial T wave changes	None
-	Diagnostic Q waves and serial T wave changes	None
-	Serial T wave changes	Upper chest pain, worse on movement, relieved partly by oxygen
-	Serial T wave changes	None
-	Diagnostic Q waves, and inverted T waves on first ECG	None
-	Diagnostic Q waves	Central
-	No ischaemic features	Central, sharp, lasted >12 hours, exertional
-	No ischaemic features	None
-	No ischaemic features	Central, tight, exertional
-	No ischaemic features	Central, tight
-	No ischaemic features	Central, tight, exertional, radiating to arm/jaw
-	No ischaemic features, no admission ECG	Sharp, exertional, relieved partly by oxygen

However, neither chest pain, nor chest pain with exclusively high risk features, was associated with raised troponin (p=0.77 and p=0.29 respectively). Raised troponin was commoner in patients with admission ECGs with diagnostic Minnesota codes for myocardial infarction (p=0.06) but there was no evidence that serial ECG changes were commoner and (p=0.39).

In exploratory analyses the associations between raised troponin and a wide range of patient characteristics were examined, including severity of airflow limitation, performance status, smoking status, usual and acute therapy, anaemia, raised inflammatory markers and symptoms suggestive of infection, and arterial blood gases. There was some evidence that diabetes, right bundle branch block, acidosis and methylxanthine therapy in patients with exacerbations may be associated with

raised troponin, while use of a long acting beta-agonist was less common in patients with raised troponin (Table 4-7).

Table 4-7 Raised troponin relative to chest pain, ECG features and selected characteristics

	>3 x LLD	>1 x LLD	≤ LLD	p-Value
Chest pain				
Any	9 (60%)	4 (44%)	111 (51%)	0.77
High risk	2 (13%)	0 (0%)	48 (22%)	0.29
New pain	6 (40%)	4 (44%)	84 (31%)	0.94
First admission ECG				
Diagnostic ECG	4 (27%)	3 (33%)	28 (13%)	0.06
Equivocal ECG	5 (33%)	3 (33%)	80 (36%)	>0.99
Sinus tachycardia	8 (53%)	7 (78%)	97 (44%)	0.14
Left bundle block	0 (0%)	0 (0%)	12 (6%)	>0.99
Right bundle block	3 (20%)	0 (0%)	12 (6%)	0.08
p-Pulmonale	2 (13%)	1 (11%)	17 (8%)	0.36
Right axis deviation	2 (13%)	1 (11%)	17 (8%)	0.36
CIIS, mean (95%CI)	20 (16-25)	17 (10-23)	15 (14-17)	0.13
Serial ECG changes	7 (50%)	4 (50%)	72 (40%)	0.39
CIIS, mean (95%CI)	1 (-3-6)	4 (-1-10)	-2 (-3-0)	0.11
Airflow limitation				
Mild	2 (20%)	0 (0%)	8 (5%)	
Moderate	2 (20%)	1 (20%)	56 (33%)	
Severe	5 (50%)	1 (20%)	59 (35%)	
Very severe	1 (10%)	3 (60%)	48 (28%)	0.19

	>3 x LLD	>1 x LLD	≤ LLD	p-Value
Performance Status (PS) when stable				
PS 0	2 (14%)	0 (0%)	9 (4%)	
PS 1	4 (29%)	1 (13%)	60 (28%)	
PS 2	4 (29%)	2 (25%)	84 (39%)	0.40
PS 3	3 (21%)	4 (50%)	50 (23%)	
PS 4	1 (7%)	1 (13%)	14 (6%)	
Long term oxygen	1 (7%)	1 (11%)	38 (17%)	0.67
Current smoker	7 (47%)	3 (33%)	105 (48%)	0.71
Diabetes	5 (33%)	1 (11%)	24 (11%)	0.05
Long acting beta agonists	7 (47%)	5 (56%)	160 (73%)	0.05
Methylxanthines	5 (33%)	4 (44%)	25 (11%)	0.002
Medical Research Council dyspnoea score (MRC) on admission				
MRC 1	0 (0%)	0 (0%)	1 (0%)	
MRC 2	0 (0%)	0 (0%)	3 (1%)	
MRC 3	2 (15%)	1 (11%)	12 (6%)	0.41
MRC 4	1 (8%)	0 (0%)	41 (19%)	
MRC 5	10 (77%)	8 (89%)	156 (73%)	
Arterial blood gases				
Acidosis	5 (33%)	3 (33%)	33 (15%)	0.04
Hypoxia	3 (20%)	1 (11%)	75 (34%)	0.24
Hypercapnia	5 (33%)	6 (67%)	95 (44%)	0.43

4.4. Discussion

One in ten patients admitted to hospital with an acute exacerbation of COPD had raised troponin, and a quarter of these also had chest pain and serial electrocardiogram changes indicative of acute coronary syndrome.

Previous studies found that raised troponin was common in exacerbation of COPD. In one consecutive case-series of 71 patients admitted with acute exacerbation of COPD 13 (18% (95% CI 11 to 29%) had raised troponin, (Baillard et al. 2003) and in a case note review of 375 patients admitted to hospital with COPD, troponin was raised in 24% (95% CI 19 to 31%) of those in whom it was measured. The former study was conducted in an intensive care setting, and in the latter troponin was measured in only half the sample, with those tested having been selected non-randomly by the treating clinician. The current case series did not consecutively recruit all admitted patients, but the sample was nonetheless very similar to that obtained in the recent BTS 2008 audit which did sample consecutive patients admitted to hospital with acute exacerbation of COPD (Table 4-2). Therefore, this case-series adds to the literature by confirming that raised troponin is common in patients admitted to hospital with exacerbation of COPD not selected for troponin testing on clinical grounds.

A priori acute coronary syndrome was defined as raised troponin, serial ECG changes indicative of ischaemia, and chest pain. One in forty patients with acute exacerbation of COPD met this definition, whereas in a previous study in patients with exacerbation of COPD, Donaldson et al estimated the prevalence as 1 in 2,500 (Donaldson et al. 2010). The previous study examined patients treated in the community whereas this was an in-patient study, which may partly account for the higher prevalence. However, there were also differences in the investigation and diagnosis of acute coronary syndrome. Donaldson et al used routine healthcare data whereas this prospective case-series obtained chest pain histories and serial ECGs on the entire sample. Coronary events can be missed even when patients present with chest pain (Collinson et al. 2000) and may be more likely to be missed when patients present to hospital with an alternative condition, such as exacerbation of COPD. None of the patients identified as having acute coronary syndrome were prescribed thrombolytic agents or high dose low molecular weight heparin suggesting that the

treating clinicians did not suspect acute coronary syndrome. As such, acute coronary syndrome may be under-diagnosed in patients with exacerbation of COPD.

Alternatively, raised troponin, chest pain and serial ECG changes may be less reliable for diagnosing acute coronary syndrome in the context of exacerbation of COPD. Cardiac troponin is a sensitive and specific marker of myocardial damage, but it is not pathognomonic for acute coronary disease (Christenson et al., with Wu et al., NACB WRITING GROUP MEMBERS and Jesse et al., NACB COMMITTEE MEMBERS 2007), and has been described following pulmonary embolism, supraventricular and ventricular tachycardia and non-cardiac surgery in patients with normal coronary arteries on angiography (Mahajan et al. 2006). Pathophysiological changes during exacerbation such as reduced right ventricular preload and increased afterload may also cause myocardial damage (O'Donnell & Parker 2006). Similarly, hypoxia, acidosis or tachycardia, all of which are found in exacerbations of COPD, might cause myocardial cell death, and raised troponin was commoner in patients with acidosis and right bundle branch block, a finding which replicated a previous report from a case note review of patients with exacerbation of COPD (Harvey & Hancox 2004)

Previous authors have suggested that central chest pain typical of myocardial infarction is rare in exacerbation of COPD (Donaldson et al. 2010), but recent chest pain was surprisingly common in this case series, frequently exertional, and occasionally radiated to the jaw. Moreover, neither chest pain, nor chest pain with features typically considered to be suggestive of cardiac ischaemia (Swap & Nagurney 2005) was associated with raised troponin. Chest pain character is only of limited prognostic value in uncomplicated chest pain (NICE 2010), and these findings suggest it may be even less useful in patients with exacerbation of COPD.

Electrocardiogram abnormalities such as Q-waves on the admission ECG were also common, a finding which is consistent with previous work demonstrating that ECG findings which predict long-term risk of myocardial infarction are commonly raised in patients hospitalised with acute exacerbation of COPD (Brekke, Omland, Smith, et al. 2008), as well as being associated with reduced FEV_1 (Sin & Man 2003). Changes in T-waves and in ST segment depression across serial ECGs were also

common. However, serial ECG changes were not associated with raised troponin in this case-series, suggesting that technical factors (eg lead position) or transient ischaemia may cause a significant proportion of serial ECG abnormalities in exacerbation of COPD.

However, 50% of patients in the sample either had known vascular disease or an estimated 10 year (Framingham) risk of a cardiac event of greater than 20%, patients with COPD are known to have an elevated risk of cardiovascular mortality and morbidity (McGarvey et al. 2007; Anthonisen et al. 2002) and two previous observational studies using routine healthcare data found that the risk of myocardial infarction was two-fold higher in patients with COPD during and immediately following acute exacerbations (Huiart et al. 2006; Donaldson et al. 2010). Furthermore, inflammation has been implicated in plaque rupture and thrombus formation (Libby 2002), and exacerbation of COPD is associated with raised CRP, Il-6 and fibrinogen, (Wedzicha et al. 2000; Hurst et al. 2006) while in a recent study conducted in a sub-group of patients from this case-series that has been reported in abstract form, platelet activation was higher during exacerbations than in the stable state (Maclay, McAllister, Mills, Newby, et al. 2009).

Therefore, although non-coronary mechanisms such as right heart strain and acidosis may cause the majority of cases of raised troponin in exacerbation of COPD, coronary mechanisms are also implicated. As such, the high prevalence in exacerbation of COPD of raised troponin, chest pain conventionally considered suggestive of ischaemia, and abnormal ECGs represent a diagnostic difficulty. Larger observational studies may identify further patient characteristics which are associated with raised troponin, but are unlikely to identify whether these are also indicative of acute coronary artery thrombosis. Indeed, given the clinical complexity only experimental studies (eg clinical trials of secondary prevention strategies) are likely to address the question of how best to manage patients with exacerbation of COPD and raised troponin.

4.4.1. Limitations

This was not a consecutive sample of patients admitted with acute exacerbation of COPD, limiting generalisability to other populations. However, this case-series

included patients from district general as well as teaching hospitals, and this sample are similar to the consecutive sample described in the 2008 British Thoracic Society audit of patients admitted to hospital with acute exacerbation of COPD (Buckingham et al. 2008). Moreover, patients were not sampled on the basis of chest pain, troponin or ECG changes making systematic bias less likely.

The troponin measurements were conducted in different laboratories using different assays rather than a single centre. However, studying patients across multiple centres was a strength of the study, a recommended method for summarising the results across multi-centre studies was employed, and results were not directly compared between centres (Apple et al. 2002).

A further limitation was that the ECGs were obtained as part of routine clinical care, in patients who were frequently acutely unwell, rather than in controlled conditions. As such, the accuracy of the coding is likely to have been reduced, particularly when evaluating the degree of ST segment changes. However, this also meant that the ECGs were representative of those encountered by clinicians treating this patient group.

4.4.2. Conclusion

Raised troponin is common in patients with exacerbation of COPD, as is chest pain and serial changes in electrocardiograms. Identifying whether patients admitted to hospital with acute exacerbation of COPD have had an acute coronary event is difficult as both chest pain and serial electrocardiogram changes are commonly found in patients without raised troponin. Experimental studies are needed to address the question of how to manage raised troponin in acute exacerbation of COPD.

5. Cross-sectional study in patients with chronic obstructive pulmonary disease: carotid-radial pulse wave velocity

5.1. Introduction

Cardiovascular disease is a common cause of death in patients with Chronic Obstructive Pulmonary Disease (COPD) (Anthonisen et al. 2002; McGarvey et al. 2007). Moreover, airflow limitation, as measured by FEV_1 predicts cardiovascular mortality even after adjusting for established cardiovascular risk factors including age, sex, smoking, cholesterol, and socioeconomic deprivation (Hole et al. 1996; Friedman et al. 1976).

Arterial stiffness is a useful non-invasive measure of vascular function, and is an independent predictor of cardiovascular events in subjects with diabetes in the general population (Laurent et al., on behalf of the European Network for Non-invasive Investigation of Large Arteries 2006). Arterial stiffness is associated with airflow limitation in healthy men (Bolton et al. 2009; Zieman et al. 2005), and has been found to be higher in COPD patients compared to controls matched on age, and sex (Sabit et al. 2007) and in male ex-smokers with COPD compared to controls matched on age, pack years smoking (Maclay, McAllister, Mills, Paterson, et al. 2009).

The mechanism by which arterial stiffness is increased in patients with COPD is unknown. One hypothesis is that impaired lung function and increased arterial stiffness in COPD may both be due to increased susceptibility to degradation of connective tissue in this group of patients. In the lung, elastin degradation leads to loss of alveolar attachments, decreased compliance, and emphysema (Shifren & Mecham 2006). While in the arteries, age-related elastin degradation is associated with increased collagen, larger thicker arteries, and increased arterial stiffness (Zieman et al. 2005).

Therefore, the aim of this chapter is to test the hypothesis that the extent of arterial stiffness is associated with the severity of emphysema in patients with COPD.

5.2. Methods

5.2.1. Patients studied

Patients with COPD were recruited from primary and secondary care. Blood pressure and arterial stiffness were measured in 177 subjects with COPD who participated in a cohort study designed to identify prognostic markers in COPD. During recruitment, ethical approval was obtained to perform high resolution computed tomography (CT) scans of chest. All subsequently enrolled subjects (n=73) subjects had CT scans. All studies were approved by Lothian Regional Ethics Committee approval, and all subjects gave written informed consent.

All subjects had a clinical history compatible with COPD, a history of risk factors (history of at least ten pack years of smoking) and evidence of chronic airflow limitation on spirometry (post bronchodilator $FEV_1/FVC < 0.70$)(23). Subjects were not taking oral anti inflammatory drugs, including corticosteroids. Subjects with systemic inflammatory diseases (e.g. rheumatoid arthritis, inflammatory bowel disease) were excluded. Cardiovascular co-morbidity was not an exclusion criterion but was recorded. Visits were performed when subjects were clinically stable ($\geq$ 4 weeks since last exacerbation as defined by a worsening of symptoms requiring intervention with antibiotic therapy or oral corticosteroids).

Height, weight, and post-bronchodilator spirometry were measured (Vitalograph Alpha Spirometer, Buckingham, England) according to ATS/ERS standards in all subjects (Miller et al. 2005). Venous blood was sampled and stored at -80 Celsius for subsequent analysis. Serum CRP concentrations were measured using a highly sensitive immunonephelometric assay (Behring BN II nephelometer, Marburg, Germany). Glucose and cholesterol were measured in the locally accredited clinical biochemistry laboratory (Olympus Analyzers, Centre Valley, USA). Oxygen saturations were measured at rest breathing air, by pulse oximetry (Nellcor Puritan Bennett Sensor, Pleasanton, USA). Individuals who underwent CT also had six minute walking tests in accordance with ATS guidelines (American Thoracic Society 2002).

5.2.2. Haemodynamic studies

Arterial stiffness and peripheral blood pressure measurements were obtained prior to spirometry and venepuncture in a quiet, temperature controlled room with subjects resting supine at 15 degrees. Patients had abstained from smoking, caffeine, and all medication on the day of the test. Systolic and diastolic blood pressure was measured in duplicate using an automated non-invasive oscillometric sphygmomanometer (Omron 705IT, Milton Keynes, UK) following a 10 min rest period.

After 30 minutes of rest, arterial stiffness was measured using carotid-radial Pulse Wave Velocity (PWV) by specifically trained staff. PWV measures the rate at which the systolic pressure wave travels to the peripheral vasculature (Section 1.4.2). Faster wave transit times reflect stiffer arteries. In this study the q-wave of a simultaneously recorded ECG was used to identify the onset of the pressure wave, and used applanation tonometry (Millar Instruments, Texas) at the carotid and radial arteries to record the pressure waveform at the peripheral site. The SphygmoCor™ system (AtCor Medical, Sydney) software applied an intersecting tangent algorithm to identify the onset of the wave. The difference in wave transit time between the carotid and radial sites was used to calculate the carotid-radial PWV.

Quality control checks were made for all measurements according to manufacturer guidelines (Atcor Medical 2008). All waveforms were reviewed, as were summary statistics for variability between waveforms. Results with a standard deviation of 15% or greater were not included in the analysis, nor were measurements with a standard deviation of 10% to 15% in which the onset of the waveform was not clearly identified. Where a patient had two or more measures which met QC criteria the mean was used.

5.2.3. CT imaging

High Resolution CT (CT) scanning of the lungs was performed at full inspiration using a 16 slice multidetector-row CT scanner (135kv, 20mAs, Toshiba Aquilion, Toshiba, Japan). Patients were coached to perform full inspiration. Contrast media was not administered. Images were reconstructed with a slice thickness of 5mm and 2.5mm increment using an FC-03 filter. Calibration of air CT density measurements was made using a background air region above the sternum. Emphysema was

quantified by in house software. Percent emphysema, also known as the pixel index or density mask, was defined as the total number of voxels with a density of less than -910 Hounsfield Units (Hu) divided by to the total number of voxels in the lung fields (27-29). Percent emphysema at -950 (Hu) and the 15th percentile point of frequency distribution of lung density were also calculated.

5.2.4. Data analysis

A univariate analysis of carotid-radial PWV on all variables of interest was performed in the sub-group who had CT of chest (Pearson's correlation and independent sample t-tests as appropriate). Multiple linear regression was used to model the association between carotid-radial PWV and percent emphysema after adjusting for potential confounders. Analyses were performed with SPSS version 14 (Illinois, USA) and graphs were drawn using R version 2.9.2 (R Foundation, Vienna, Austria).

5.3. Results

Carotid-radial PWV was performed in 177 COPD patients, with satisfactory measurements obtained in 157 patients. The full cohort (n=157) and CT sub-group (n=73) were similar for all clinical, laboratory, haemodynamic and spirometric characteristics (Table 5-1).

Table 5-1 Characteristics in patients with and without CT measures

	All subjects	Non-CT	CT subjects
n	157	84	73
Age	67.9 (7.6)	67.9 (8.0)	67.9 (7.2)
Male	92 (59%)	46 (55%)	46 (63%)
Height(cm)	166.5 (10.0)	165.4 (9.5)	167.9 (10.4)
Weight(kg)	71.3 (18.1)	68.32 (17.4)	74.6 (18.4)
BMI (kg/m^2)	25.6 (5.6)	24.9 (5.5)	26.4 (5.8)
Oxygen saturations*	96 (94-97)	96 (95-98)	96 (94-97)
SGRQ total score*	50 (33-63)	50 (35-67)	4 9 (32-61)
Pack years smoking*	40 (30-56)	43 (25-50)	40 (30-52)
Current smoker	62 (39%)	38 (45%)	24 (33%)
Chronic bronchitis	74 (50%)	37 (44.6%)	37 (58%)
Ankle oedema	37 (24%)	21 (25%)	16 (22%)
Inhaled Corticosteroid	103 (66%)	54 (64%)	49 (67%)
Long Acting Beta Agonist	83 (53%)	47 (56%)	36 (49%)
History of ischaemic heart disease	32 (20%)	19 (23%)	13 (18%)
History of hypercholesterolaemia	21 (13%)	11(13%)	10 (14%)
History of diabetes	3 (2%)	1(1%)	2 (3%)
Spirometry			
FEV_1 (L)	1.29 (0.58)	1.21 (0.56)	1.37 (0.59)
FEV_1/FVC	49 (14)	49 (15)	50 (13)

	All subjects	Non-CT	CT subjects
n	157	84	73
FEV_1 percent predicted	51 (20)	50 (20)	53 (20)
Haemodynamic			
Heart Rate	69 (11)	69 (10)	69 (11)
Systolic Pressure (mmHg)	144 (23)	144 (24)	144 (21)
Diastolic Pressure (mmHg)	81 (11)	80 (11)	81 (12)
Pulse Pressure	64(19)	64 (20)	63 (17)
Mean arterial pressure	102(13)	101 (12)	102 (13)
Carotid-radial Pulse Wave Velocity (m/s)	8.69 (1.51)	8.55 (1.52)	8.85 (1.50)
Laboratory			
Glucose (mmol/l)	6.12 (1.28)	6.03 (1.23)	6.13 (1.33)
Cholesterol:HDL ratio	3.74 (1.09)	3.71 (1.14)	3.77 (1.04)
White cell count	7.48 (2.10)	7.43 (2.28)	7.55 (1.87)
Neutrophil count	4.79 (1.67)	4.91 (1.88)	4.65 (1.40)
Platelet count	262 (66)	260 (67)	263 (65)
CRP (mg/L)*	3.66 (1.87-7.25)	3.76 (1.98 – 8.32)	3.48 (1.67-6.72)

Values represent Mean (SD), except * median (IQR), and % count (percentage).

In the full cohort carotid-radial PWV was higher in men, and there were statistically significant associations between carotid-radial PWV and height, oxygen saturations, FEV_1 percent predicted, FEV_1/FVC ratio, heart rate, and blood pressure. There was no association between CRP and PWV, or between smoking pack years and carotid-radial PWV (Table 5-2, Table 5-3 and Figure 5-1).

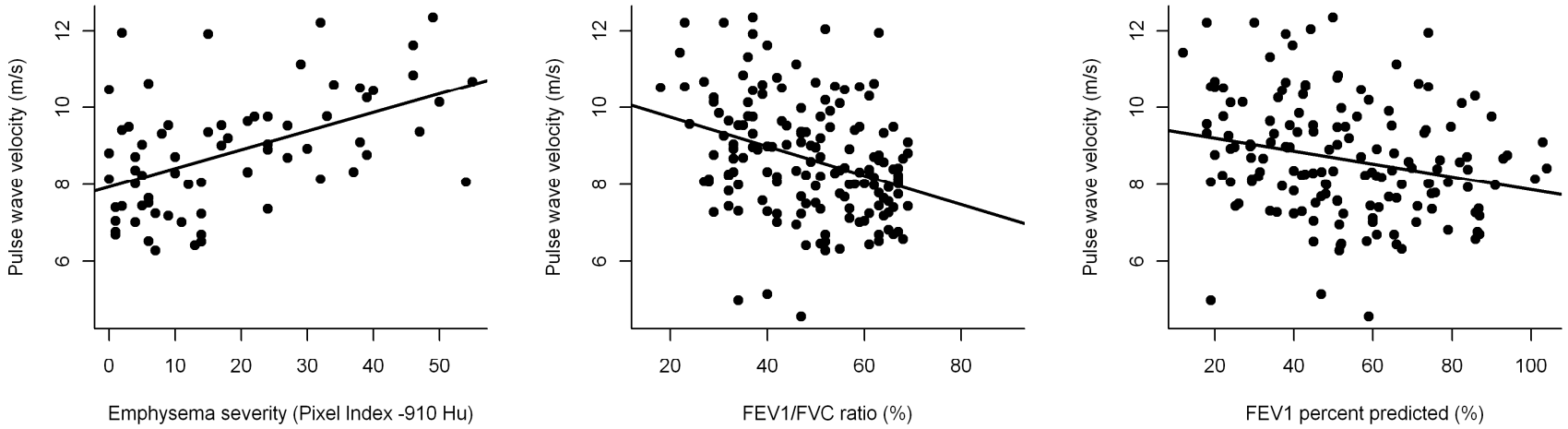

Figure 5-1 Association of carotid-radial pulse wave velocity with emphysema severity, the FEV_1/FVC ratio and FEV_1 percent predicted

In the sub-group of patients who underwent CT, height, body mass index (BMI), heart rate, diastolic pressure, FEV_1 percent predicted, and FEV_1/FVC, were associated with pulse wave velocity on univariate analysis (Table 5-2). Carotid-radial PWV was higher in COPD patients with severe and very severe COPD (GOLD stage 3 and 4) than in those with mild and moderate disease (GOLD stage 1 and 2, 9.05m/s versus 8.37 m/s p=0.004), and was greater in men than women (0.99 m/s p=0.006), but there was no difference in carotid-radial PWV between subjects with or without a history of ischaemic heart disease or between current and ex-smokers (Table 5-3). Pack years smoking history was not associated with PWV (r=-0.18, p= 0.13), nor with emphysema severity (r=- 0.96, p=0.43). No relationship was found between hsCRP and PWV, nor between leukocytes and carotid-radial PWV (Table 5-2).

Table 5-2 Associations between continuous variables and carotid-radial PWV in the full cohort and CT subgroup (Pearson's correlations)

	All Subjects n=157		CT Subjects n=73	
	r value	p value	r value	p value
Age	-0.013	0.868	-0.137	0.246
Clinical				
Height(cm)	0.266	0.001	0.279	0.017
Weight (kg)	-0.020	0.806	-0.332	0.332
BMI (kg/m^2)	-0.155	0.052	-0.280	0.016
Oxygen saturations	-0.167	0.039	-0.114	0.336
SGRQ total score	0.073	0.366	-0.072	0.547
Pack years smoking	-0.023	0.780	- 0.180	0.132
Six minute walk distance (m)	n/a	n/a	0.074	0.576

	All Subjects n=157		CT Subjects n=73	
	r value	p value	r value	p value
FEV_1 (l)	-0.012	0.881	0.029	0.805
FEV_1/FVC	-0.295	<0.001	-0.419	0.001
FEV_1 percent predicted	-0.208	0.009	-0.243	0.038
Glucose (mmol/l)	0.138	0.085	-0.024	0.843
Cholesterol:hdl ratio	-0.048	0.562	-0.082	0.496
Log CRP	-0.63	0.435	-0.199	0.093
White cell count	0.023	0.772	0.023	0.846
Neutrophil count	0.039	0.634	-0.026	0.828
Platelet count	-0.042	0.615	<0.001	>0.999
Heart Rate	0.246	0.002	0.231	0.049
Systolic Pressure (mmHg)	0.180	0.024	0.125	0.293
Diastolic Pressure (mmHg)	0.403	<0.001	0.367	0.001
Mean Arterial Pressure (mmHg)	0.332	<0.001	0.282	0.016
Pulse Pressure (mmHg)	-0.027	0.740	-0.095	0.423
Percent emphysema				
- 950 Hounsfeld units	n/a	n/a	0.471	<0.001
- 910 Hounsfeld units	n/a	n/a	0.476	<0.001
15th Percentile density (Hu)	n/a	n/a	- 0.409	<0.001

Table 5-3 Mean Difference in carotid-radial PWV between dichotomous groups in the full cohort and CT subgroup (t-tests)

	Full Cohort n=157		CT Subgroup n=73	
	m/s	p value	m/s	p value
Gender	0.783	0.001	0.99	0.006
Current Smoking	0.181	0.464	0.30	0.418
Chronic Bronchitis	0.338	0.173	0.25	0.509
Ankle Oedema	0.369	0.195	0.05	0.906
Inhaled Corticosteroid	0.023	0.929	0.42	0.322
Long Acting Beta Agonist	0.156	0.521	0.47	0.182
Ischaemic Heart Disease	0.351	0.242	0.34	0.480
Hypercholesterolaemia	0.591	0.095	0.80	0.124

In adjusted analyses, severity of emphysema (r^2=0.13, p=0.002) and mean arterial pressure (r^2 =0.08, p=0.043) were the factors most closely associated with PWV, with BMI and gender almost reaching statistical significance (Table 5-4).

Table 5-4 PWV regressed on gender, height, body mass index, heart rate, mean arterial blood pressure, FEV_1 percent predicted and percent emphysema

	Beta	Standard error	Partial r^2	p value
Male gender	0.381	0.414	0.01	0.36
Height (m)	0.017	0.018	0.01	0.36
Body Mass Index (kg/m^2)	-0.049	0.028	0.05	0.09
Heart Rate	0.016	0.016	0.06	0.05
Mean Arterial Pressure (mmHg)	0.026	0.013	0.06	0.04
Log CRP	-0.431	0.34	0.02	0.21
FEV_1 percent Predicted	0.652	0.95	0.01	0.50
Percent emphysema	4.358	1.525	0.11	0.006

CT subjects n= 71, global significance test (ANOVA) $p<0.001$, $r^2 =0.409$

In sensitivity analyses, carotid-radial PWV was associated with severity of emphysema regardless of whether percent emphysema was calculated using the -910 Hu, -950Hu cut-offs or whether the 15th percentile was used, and after additionally adjusting for age, smoking status and pack years smoking.

5.4. Discussion

Emphysema severity was associated with arterial stiffness, as measured by carotid-radial pulse wave velocity independent of cigarette smoking in patients with COPD. The association was also independent of age, sex, blood pressure, hsCRP, dyslipidaemia, inflammation, hypoxaemia, and airflow limitation.

Carotid-femoral pulse wave velocity, a distinct measure of arterial stiffness, predicts mortality in a wide range of settings, and has previously been found to be higher in COPD patients than in controls (Sabit et al. 2007; Maclay, McAllister, Mills, Paterson, et al. 2009). The finding from this study, that arterial stiffness as measured

by carotid-radial pulse wave velocity is associated emphysema severity independent of FEV_1 percent predicted, suggests that COPD patients with an emphysematous phenotype may be at increased cardiovascular risk compared to patients with a non-emphysematous phenotype, and longitudinal studies are now required.

Cigarette smoke exposure has a causal relationship with both COPD and cardiovascular disease. It was therefore important to address smoking as a potential confounder, and this was done by adjusting for smoking status and pack-years. Pack years is the most widely used measure for assessing lifetime cigarette smoke exposure, but is based upon self-recall over several years and as such inaccurate reporting is likely. It is unlikely that error in reported smoking was differential by pulse wave velocity, but non-differential error in the measurement of cigarette smoke exposure may explain why no association was found between pack-years and emphysema and between pack-years and PWV in this study, as well as between pack-years and these measures in previous studies (Sabit et al. 2007; Makita et al., the Hokkaido COPD Cohort Study Group 2007). Consequently, residual confounding by cigarette smoke exposure needs to be considered as a potential explanation for the observed association between carotid-radial PWV and percent emphysema.

However, the association between carotid-radial PWV and percent emphysema was independent of FEV_1 which is also likely to be a marker of cigarette exposure. In addition, the patients studied had substantial smoking histories and were susceptible to cigarette smoke as evidenced by clinical COPD. Consequently variability in smoke exposure within this group might not be as important as in unselected samples. Moreover, the association between emphysema and PWV was strong, and would be unlikely to be entirely abolished even if a more accurate measure of cigarette smoke exposure were available.

In a previous case-control study of carotid-femoral PWV in COPD, there was an association between Il-6 and carotid-femoral PWV and the authors postulated that the increased systemic inflammation seen in COPD may be responsible for the observed increase in arterial stiffness (Sabit et al. 2007). In this larger cohort there was no association between carotid-radial PWV and hsCRP, whose release is

stimulated by Il-6. Nor was there an association between emphysema severity and hsCRP. As such, the results of this study do not support the hypothesis that systemic inflammation is an important cause of arterial stiffness in patients with COPD. Nonetheless, a different measure of PWV was used than by Sabit et al (Sabit et al. 2007), and there may be other circulating inflammatory factors, oxidised lipids or proteins which, through their effect on endothelium and smooth muscle, link the lung inflammation and oxidative stress, which are found in patients with emphysema, to the development of arterial stiffness.

Another possible mechanism to explain the association between emphysema severity and arterial stiffness is hypoxia. There was no association between pulse oximetry oxygen saturations and arterial stiffness after controlling for other variables. Although pulse oximetry does not directly measure tissue hypoxia, it seems unlikely, given the relatively large regression co-efficient found, that tissue hypoxia could completely account for the observed association between emphysema and carotid-radial PWV, even with a measure such as mixed venous oxygenation.

There are a number of pathological features common to arterial stiffness and emphysema which suggest that, in some individuals with COPD, there may be an acquired or inherited tendency to develop emphysema and arterial stiffness, as was discussed in Section 1.4.5.

5.4.1. Limitations

In previous studies increased BMI was associated with increased arterial stiffness (Mitchell et al. 2005), presumably as a result of the effects of obesity and the metabolic syndrome. Instead, in the current study, low BMI was associated with increased PWV on univariate testing, and was of borderline significance on multivariable testing (Table 5-4). However, low BMI is a marker of more severe COPD (Celli et al. 2004) and is likely to reflect a more catabolic state, which may explain this apparently contradictory finding, as well as explaining why other metabolic factors such as hyperglycaemia and hypercholesterolaemia were not significantly associated with PWV in these patients.

CT scanning was not performed in all patients, and those who had CT scanning were not selected randomly. However, patients with CT measures were very similar to

those without, and in particular were very similar in terms of PWV and FEV_1. As such, selection bias is unlikely to account for the observed association.

PWV was measured via the carotid-radial method, which is associated with coronary artery plaque burden, and increases linearly with age (Hall et al., with McEniery et al., Yasmin 2005; McLeod et al. 2004). Using this technique meant PWV could be performed with subjects lying supine at 15 degrees which meant that patients with severe dyspnoea could be included in the study. However, carotid-femoral PWV (in which the tonometer is placed over the femoral artery) rather than carotid-radial PWV is the recognised "Gold standard" measure of arterial stiffness (Laurent et al., on behalf of the European Network for Non-invasive Investigation of Large Arteries 2006). No measure of arterial stiffness has been validated as a marker of cardiovascular risk in a COPD population, but carotid-femoral PWV predicts cardiovascular risk in longitudinal studies in a variety of conditions (Laurent et al., on behalf of the European Network for Non-invasive Investigation of Large Arteries 2006). As such, had the same association between PWV and emphysema been shown using this measure rather than carotid-radial, there would have been a stronger case for longitudinal studies to examine emphysema severity as a predictor of cardiovascular mortality.

Carotid-radial PWV measures the travel of the wave-form from the ascending aorta to the radial artery, while carotid-femoral PWV measures travel of the wave-form from the ascending aorta to the iliac artery. There is considerable heterogeneity across the vascular tree, the aorta differs considerably along its length, the relative amount of elastin decreases, and collagen and smooth muscle increase as the vessel travels distally (Nichols & O'Rourke 1990; Duprez et al. 2007). Therefore, to further explore whether elastin degradation is fundamental to the association between emphysema, FEV_1 and aortic stiffness a local measure of arterial stiffness in the proximal aorta may provide additional information. This is addressed in Chapter 6.

5.4.2. Conclusion

Severity of emphysema correlates with carotid-radial PWV a measure of arterial stiffness in patients with COPD. This association may be due to systemic effects of COPD (inflammation, oxidative stress and hypoxia), to environmental factors such

as pollution, or to a shared susceptibility to degradation of elastin and other components of the extra-cellular matrix in both systemic arteries and the lung. Subsequent chapters explore whether different regions of the arterial tree have different relationships with lung function and emphysema severity.

6. Cross sectional study in multi-centre general population sample: proximal aortic distensibility

6.1. Introduction

Arterial stiffness, as measured by carotid-femoral PWV, predicts cardiovascular mortality independent of age, sex, smoking history, cholesterol, and mean arterial blood pressure, and is associated with coronary atheroma burden and known cardiovascular risk factors such as smoking (Boutouyrie et al. 2002; Mattace-Raso et al. 2006; Willum Hansen et al. 2006). Carotid-femoral PWV was found to be higher in COPD patients than in controls matched on age and sex (Sabit et al. 2007), and to be associated with FEV_1 in healthy men (Bolton et al. 2009; Zureik, Benetos, et al. 2001).

Emphysematous lung and stiffened arteries share a number of pathophysiological features, including elastin degradation, abnormal collagen remodelling (Finlay et al. 1996; Zieman et al. 2005), and enhanced proteolytic activity (Wallace et al., with Yasmin 2005; Finlay et al. 1997). Loss of skin elasticity is also associated with emphysema severity independent of age and smoking history (Patel et al. 2006). Therefore there may be a shared susceptibility to connective tissue degradation in both the artery and lung leading to arterial stiffening and emphysema respectively.

Associations between emphysema severity on CT and vascular measures have been reported. Impaired flow mediated dilation (a marker of endothelial vasomotor function) is associated with emphysema severity on CT (Barr, Mesia-Vela, et al. 2007), and in Chapter 5, an association was reported between emphysema severity and carotid-radial pulse wave velocity.

There is considerable heterogeneity across the vascular tree, the aorta differs considerably along its length, the relative amount of elastin decreases, and collagen and smooth muscle increase as the vessel travels distally (Nichols & O'Rourke 1990; Duprez et al. 2007). It is not known whether emphysema severity or FEV_1 is associated with increased stiffness in central elastic arteries.

Therefore, the aim of this chapter is to test the hypothesis that arterial stiffness in the proximal aorta, measured via reduced distensibility of the ascending aorta on magnetic resonance (MR), a well-validated measure of local central arterial stiffness

(Oliver & Webb 2003; Malayeri et al. 2008; Laurent et al., on behalf of the European Network for Non-invasive Investigation of Large Arteries 2006), is associated with severity of emphysema and reduced FEV_1 in a large population-based cohort, including participants with airflow limitation.

6.2. Methods

6.2.1. Population studied

The Multi-Ethnic Study of Atherosclerosis (MESA) is a multi-centre prospective cohort study designed to investigate sub-clinical cardiovascular disease in individuals without clinical cardiovascular disease (Bild et al. 2002). In 2000 to 2002, MESA recruited 6,814 men and women aged 45 to 84 from six U.S. communities: Forsyth County, NC; Northern Manhattan and the Bronx, NY; Baltimore City and Baltimore County, MD; St. Paul, MN; Chicago, IL; and Los Angeles, CA. MESA participants were European-American white, African-American, Hispanic, or Asian-American (mostly of Chinese origin). Exclusion criteria were clinical cardiovascular disease (physician diagnosis of heart attack, stroke, transient ischemic attack, heart failure, angina, current atrial fibrillation, and any cardiovascular procedure), weight >300 lbs, pregnancy or impediment to long-term participation (Bild et al. 2002). MESA protocols and all studies described herein have been approved by the Institutional Review Boards of all collaborating institutions, and this analysis was approved by Lothian Research Ethics Committee.

The MESA-Lung Study enrolled 3,965 MESA participants, of 4,483 sampled randomly from among those who consented to genetic analyses, underwent baseline measures of endothelial function, and attended an examination during the MESA-Lung recruitment period in 2004-2006 (99%, 89%, and 91% of the MESA cohort, respectively). Chinese-Americans were over sampled to improve the precision of estimates for this group. For the current analysis related to obstructive lung disease, 322 (9%) participants with restrictive spirometry were excluded. Restrictive spirometry was defined as a FVC less than the lower limit of normal (LLN) with a forced expiratory volume in one second FEV_1/FVC ratio above 0.70 (Hankinson et al. 1999).

6.2.2. Aortic distensibility

Consenting participants underwent a cardiac MR scan in 2000-2002. The protocol, its reliability and characteristics of MESA participants with and without MR measures have been previously described (Malayeri et al. 2008; Cheung et al. 2004). All imaging was performed on 1.5 T magnets with a 4-element phased-array surface coil positioned anteriorly and posteriorly, electrocardiographic gating, and brachial artery blood pressure monitoring.

Aortic cross sectional area at the level of the right pulmonary artery during systole and diastole were calculated using an automated contour routine using the software FLOW (Medis, Netherlands). Brachial blood pressure was measured with the participant supine in the MR scanner before and after the scan. Proximal aortic distensibility was calculated as 1000 x (maximum area – minimum area) / (minimum area x brachial pulse pressure). Left ventricular stroke volume was calculated as previously described (Heckbert et al. 2006).

6.2.3. Spirometry

Spirometry was conducted in 2004-2006 in accordance with the ATS/ERS guidelines (Miller et al. 2005). All participants performed at least three acceptable manoeuvres. Tests were conducted using a dry-rolling-sealed spirometer and software that performed automated quality checks as manoeuvres were performed (Occupational Marketing, Inc., Houston, TX). All spirometry exams were reviewed by one investigator and each test was graded for quality, as previously described (Hankinson et al. 2009). Participants with no acceptable curves were excluded from spirometry analyses. Airflow limitation was defined as pre-bronchodilator $FEV_1/FVC \leq 0.7$ and FEV_1 <80% of predicted. The ICC of both the FEV_1 and the FVC on random 10% repeat testing was 0.99.

6.2.4. CT emphysema measurement

Quantitative measures of emphysema on CT scan were performed on the lung fields of MESA cardiac CT scans, which imaged approximately 70% of the lung volume from the carina to the lung bases. Cardiac CT scans were performed at full inspiration on multi-detector (MD) and electron-beam CT scanners in 2000-02 following a standardized protocol (Carr et al. 2005). Two scans were performed on

each participant; the scan with the higher air volume was used for analyses except in cases of discordant scan quality, in which case the scan with higher quality scan was used (Hoffman et al. 2009).

Image attenuation was assessed using modified Pulmonary Analysis Software Suite at a single reading centre by trained readers without knowledge of other participant information. Attenuation of air was also measured outside the chest and in the right and left main bronchi. Percent emphysema was defined as the percentage of the total voxels in the lung which fell below -910 Hu. The ICC on blinded re-reads was 0.94. Percent emphysema measures from the carina to lung base are highly correlated (r=0.99) with full-lung measures on the same full-lung scans in smokers. Emphysema measures from MESA cardiac scans correlated with full-lung scans (e.g., r=0.93 on MDCT scanners) (Hoffman et al. 2009).

6.2.5. Potential confounders

Age, gender, race/ethnicity, educational attainment, and medical history were self-reported. Current smoking was defined as self-report of a cigarette in the last 30 days or urinary cotinine level at the time of CT exam greater than 100 ng/ml (Immulite 2000 Nicotine Metabolite Assay; Diagnostic Products Corp., Los Angeles, CA).

Asthma was defined as self-report of physician-diagnosed asthma before age 45 years in order to avoid over-correction for COPD misdiagnosed as asthma above that age, which is common and differential by gender (Chapman et al. 2001).

Height, weight and resting blood pressure were measured using standard techniques, the latter with the Dinamap Monitor PRO 100 (Critikon, Tampa, FL) automated oscillometric device (Ni et al. 2006). Hypertension was defined as a systolic blood pressure >140 mm Hg, a diastolic blood pressure >90 mmHg, or currently taking medications for BP control (Chobanian et al., the National High Blood Pressure Education Program Coordinating Committee 2003).

Glucose and lipids were measured after a 12-h fast. The presence of diabetes mellitus was based on self-reported physician diagnosis, use of insulin and/or oral hypoglycemic agent, or a fasting glucose value >126 mg/dL. Serum glucose after 12-hour fast was measured by rate reflectance spectrophotometry on the Vitros

analyzer (Johnson & Johnson Clinical Diagnostics, Inc., Rochester, NY). Total cholesterol was measured using a cholesterol oxidase method (Roche Diagnostics), as was HDL after precipitation of non-HDL cholesterol with magnesium/dextran, triglycerides using Triglyceride GB reagent (Roche Diagnostics). LDL cholesterol was calculated in plasma specimens having a triglyceride value <400 mg/dl using the formula of Friedewald et al (Friedewald et al. 1972).

6.2.6. Statistical analysis

Demographics and medical characteristics were tabulated by respiratory condition. Among individuals without self-reported asthma before age 45, participants with normal lung function and with various degrees of severity of severity of airflow limitation were compared. Multiple linear regression of proximal aortic distensibility on lung density and lung function was performed. Analyses adjusted for study site, age, race/ethnicity, gender, height, body mass index, cigarette smoking status, pack years, diabetes, hypertension, educational attainment, serum low density lipoprotein, high density lipoprotein, and glucose concentration, antihypertensive therapy, and lipid lowering therapy.

Sensitivity analyses were performed using percent emphysema measures corrected for both outside and inside air. Interactions were tested with multiplicative terms in regression models. Generalised additive models with loess smoothing functions for continuous variables were used to test for non-linearity and to allow for the flexible specification of relationships. Smoothing functions did not improve model fit of lung function and lung density, however, and terms were treated as linear. Analyses were performed with SPSS version 14 (Illinois, USA) and R 2.6.2 (R Foundation, Vienna, Austria). All p-values were two-tailed with $p < 0.05$ considered statistically significant.

6.3. Results

Of the participants in the MESA Lung Study with valid spirometry measures and without restrictive lung disease, 1,917 had proximal aortic distensibility MR measures (Figure 6-1).

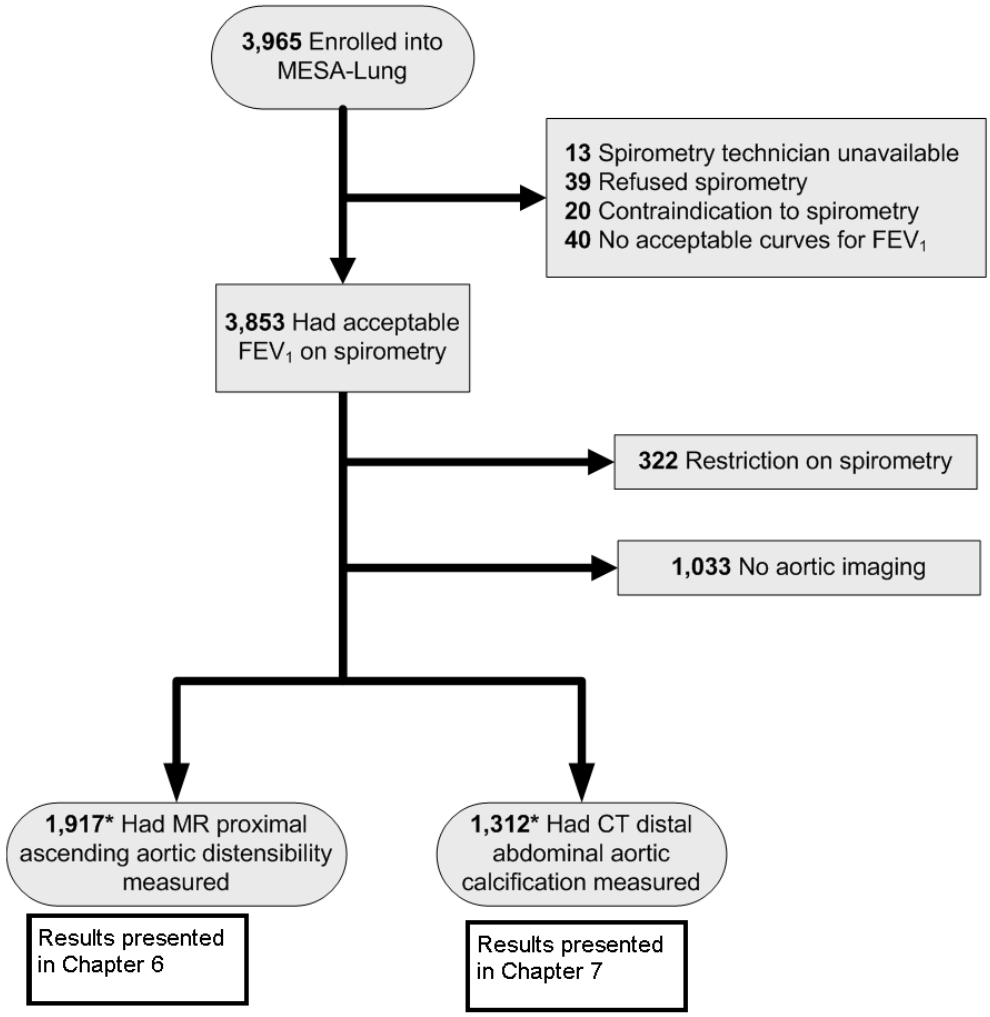

Figure 6-1 Flow-chart of inclusion/exclusion in study

Those with proximal aortic distensibility MR measures were younger and less likely to have hypertension and diabetes but were otherwise similar to those without such measures (Table 6-1).

Participants with proximal aortic distensibility MR measures were on average 60 years old and 47.1% were male. Thirty-eight percent were Caucasian, 15.9% were Chinese, 28.6% African American, and 17.8% were Hispanic. Median proximal aortic distensibility was 0.19 (interquartile range 0.11 to 0.24) $mmHg^{-1}$. Ten percent of participants had airflow limitation (Table 6-1). Those with airflow limitation were older, more likely to be male and to have hypertension, diabetes, chronic bronchitis and a history of smoking (Table 6-2).

Table 6-1 Characteristics of participants with and without proximal aortic distensibility measures

	Proximal aortic distensibility not measured	Proximal aortic distensibility measured
N	1613	1917
Age, mean (SD), years	63 (10)	60 (10)
Gender – male, n (%)	832 (51.6)	903 (47.1)
Height, mean (SD), cm	166 (10)	167 (10)
BMI, mean (SD), kg/m^2	28 (6)	27 (5)
Ethnicity, n (%)		
Caucasian	511 (31.7)	722 (37.7)
Chinese	281 (17.4)	304 (15.9)
African-American	373 (23.1)	549 (28.6)
Hispanic	448 (27.8)	342 (17.8)
Smoking status, n (%)		
Never Smoked	725 (44.9)	944 (49.2)
Ex-smoker	649 (40.2)	718 (37.5)
Current Smoker	239 (14.8)	255 (13.3)
Pack Years, median (IQR)	19 (7-35)	17 (7-35)
Spirometry, mean (SD), %		
FEV_1 percent predicted	96 (18)	96 (17)
FVC percent predicted	98 (15)	98 (14)
FEV_1/FVC ratio	74 (9)	75 (9)
MRC Bronchitis, n (%)	120 (7.5)	154 (8.1)

	Proximal aortic distensibility not measured	Proximal aortic distensibility measured
CT percent emphysema, median (IQR), %	14.3 (7.3-23.6)	15.3 (7.9-25.6)
Asthma (self reported, aged <45)	115 (7.1)	164 (8.6)
Self reported, n (%)		
Hypertension	727 (45.1)	738 (38.5)
Diabetes	207 (12.8)	159 (8.3)
Antihypertensive medication	593 (36.8)	627 (32.7)
Lipid Lowering Therapy	270 (16.7)	278 (14.5)
BP, mean (SD), mmHg		
Systolic Blood Pressure	127 (20)	123 (19)
Diastolic Blood Pressure	72 (10)	72 (10)
Pulse Pressure	55 (16)	51 (15)
Heart Rate, mean (SD), beats/min	63 (9)	63 (9)
Lipids, mean (SD), mg/dl		
LDL Cholesterol	118 (31)	118 (30)
HDL Cholesterol	50 (15)	52 (15)
Triglycerides	135 (79)	126 (89)
CRP, median (IQR), mg/L	1.83 (0.83-4.05)	1.64 (0.71-3.76)

Table 6-2 Characteristics of participants with proximal aortic distensibility measures, stratified by respiratory status/condition

	Normal spirometry without self-reported asthma	Self-reported Asthma aged<45 years	FEV_1/FVC <0.7 and FEV_1 percent predicted ≥ 80%	FEV_1/FVC <0.7 and FEV_1 percent predicted 50% to 80%	FEV_1/FVC <0.7 and FEV_1 percent predicted ≤ 50%
N	1375	164	230	128	20
Age, mean (SD), years	59 (9)	58 (10)	66 (10)	63 (9)	65 (7)
Gender – male, n (%)	606 (44.1)	67 (40.9)	149 (64.8)	68 (53.1)	13 (65)
Height, mean (SD), cm	166 (10)	167 (10)	170 (10)	169 (10)	168 (10)
BMI, mean (SD), kg/m^2	28 (5)	28 (5)	26 (4)	26 (4)	29 (6)
Caucasian	461 (33.5)	70 (42.7)	118 (51.3)	66 (51.6)	7 (35)
Chinese	248 (18.0)	15 (9.1)	29 (12.6)	9 (7.0)	3 (16)
African-American	397 (28.9)	50 (30.5)	59 (25.7)	38 (29.7)	5 (25)
Hispanic	269 (19.6)	29 (17.7)	24 (10.4)	15 (11.7)	5 (25)
Never Smoked	733 (53.3)	87 (53.0)	90 (39.1)	33 (25.8)	1 (5)
Ex-smoker	488 (33.5)	55 (33.5)	106 (46.1)	60 (46.9)	9 (45)
Current Smoker	154 (11.2)	22 (13.4)	34 (14.8)	35 (27.3)	10 (50)
Pack Years, median (IQR)	15 (6-32)	15 (6-28)	24 (11-47)	29 (14-47)	52 (27-68)
FEV_1 percent predicted, mean (SD), %	100 (14)	85 (18)	96 (11)	70 (9)	40 (9)
FVC percent predicted, mean (SD), %	98 (13)	94 (16)	109 (13)	86 (12)	67 (16)
FEV_1/FVC ratio, , mean (SD), %	79 (5)	70 (10)	66 (4)	62 (7)	47 (13)
MRC Chronic Bronchitis, n (%)	92 (6.7)	26 (15.9)	18 (7.8)	12 (9.5)	6 (30.0)
CT Percentage Emphysema, median (IQR),%	14 (7-22)	17 (10-27)	25 (15-36)	18 (10-32)	27 (10-33)

	Normal spirometry without self-reported asthma	Self-reported Asthma aged<45 years	FEV_1/FVC <0.7 and FEV_1 percent predicted ≥ 80%	FEV_1/FVC <0.7 and FEV_1 percent predicted 50% to 80%	FEV_1/FVC <0.7 and FEV_1 percent predicted ≤ 50%
Hypertension	519 (37.7)	62 (37.8)	90 (39.1)	58 (45.3)	9 (45)
Diabetes	119 (8.7)	10 (6.1)	13 (5.7)	12 (9.4)	5 (25)
Antihypertensive medication	437 (31.8)	54 (32.9)	77 (33.5)	50 (39.1)	9 (45)
Lipid Lowering Therapy	197 (14.3)	21 (12.8)	39 (17.0)	17 (13.3)	4 (20)
Systolic BP, mean (SD), mmHg	123 (19)	123 (19)	123 (19)	122 (20)	128 (16)
Diastolic BP, mean (SD), mmHg	72 (10)	72 (9)	71 (10)	70 (11)	72 (8)
Pulse pressure. mean (SD), mmHg	51 (15)	51 (16)	52 (15)	52 (15)	56 (13)
Heart rate, mean (SD), bpm	63 (9)	63 (8)	60 (9)	62 (10)	69 (14)
LDL Cholesterol, mean (SD), mg/dl	119 (29)	116 (33)	114 (30)	115 (32)	116 (29)
HDL Cholesterol, mean (SD), mg/dl	52 (15)	53 (15)	51 (15)	51 (15)	46 (9)
Triglycerides, mean (SD), mg/dl	129 (93)	128 (81)	109 (56)	124 (97)	136 (61)
CRP, median (IQR), mg/L	1.61	1.79	1.5	2.09	5.18

6.3.1. Lung function and proximal aortic distensibility

Proximal aortic distensibility was not associated with FEV_1 after adjusting for study centre, age, sex, race/ethnicity, height, and BMI (-0.02 $mmHg^{-1}$; 95% CI -0.15 to 0.11 $mmHg^{-1}$, p =0.75) or after additionally adjusting for cigarette smoking status, pack years, diabetes, hypertension, educational attainment, serum low density lipoprotein, high density lipoprotein, and glucose concentration, antihypertensive therapy, and lipid lowering therapy (-0.04 $mmHg^{-1}$; 95% CI -0.16 to 0.09, p=0.60). Results for FVC, and the FEV_1/FVC ratio were similarly null (Table 6-3).

6.3.2. Airflow limitation and proximal aortic distensibility

Similarly, reduced proximal aortic distensibility was not evident in participants with moderate or severe airflow limitation, indeed compared to participants with normal lung function, proximal aortic distensibility was higher for those with moderate airflow limitation (0.24 $mmHg^{-1}$; 95% CI 0.02 to 0.46 $mmHg^{-1}$) and severe airflow limitation (0.09 $mmHg^{-1}$; 95% CI -0.44 to 0.62 $mmHg^{-1}$).

Table 6-3 Associations of proximal aortic distensibility, lung function and percent emphysema

Exposure	Increase in Aortic Distensibility ($mmHg^{-1}$) per one unit increase in Exposure (95% CI)	p value
FEV_1 (litres)		
Model 1	-0.02 (-0.15 to 0.11)	0.75
Model 2	-0.04 (-0.16 to 0.09)	0.60
FVC (litres)		
Model 1	0.02 (-0.09 to 0.13)	0.29
Model 2	0.00 (-0.88 to 0.45)	0.95
FEV_1/FVC (ratio)		
Model 1	-0.35(-1.00 to 0.30)	0.30
Model 2	-0.21 (-27.26 to 6.51)	0.53

Model 1: adjusted for study site, age, race, gender, height, and body mass index. Model 2: adjusted for model 1 and heart rate, cigarette smoking status, pack years, diabetes, hypertension, educational attainment, serum low density lipoprotein, high density lipoprotein, and glucose concentration, antihypertensive therapy, lipid lowering therapy and left ventricular stroke volume.

6.3.3. Percent emphysema and proximal aortic distensibility

Proximal aortic distensibility was not associated with percent emphysema after adjusting for study site, age, race/ethnicity, gender, height, and body mass index, nor after additionally adjusting for study site, age, race/ethnicity, gender, height, body mass index, cigarette smoking status, pack years, diabetes, hypertension, educational attainment, serum low density lipoprotein, high density lipoprotein, and glucose concentration, antihypertensive therapy, lipid lowering therapy and scanner type and protocol (0.03 $mmHg^{-1}$; 95% CI -0.02 to 0.09 $mmHg^{-1}$, p=0.19).

6.3.4. Sensitivity Analyses

Sensitivity analyses limited to participants who had smoked greater than 10, 20 and 50 pack-years produced similar results. Exclusion of participants with asthma diagnosed before the age of 45 did not affect the results; neither did exclusion of participants with any diagnosis of asthma, nor use of CT percent emphysema measures corrected for outside air or airways air, or use of the 15th percentile point. Additional adjustment for self-reported use of bronchodilators, steroids, or methylxanthines had little impact on the results. There was no evidence for effect modification on an additive scale by gender, race/ethnicity, smoking status, study site, CT scanner type or severity of airflow limitation on spirometry. Nor was there any evidence of departure from linearity when explored using generalised additive models of proximal aortic distensibility on FEV_1 (Figure 6-2).

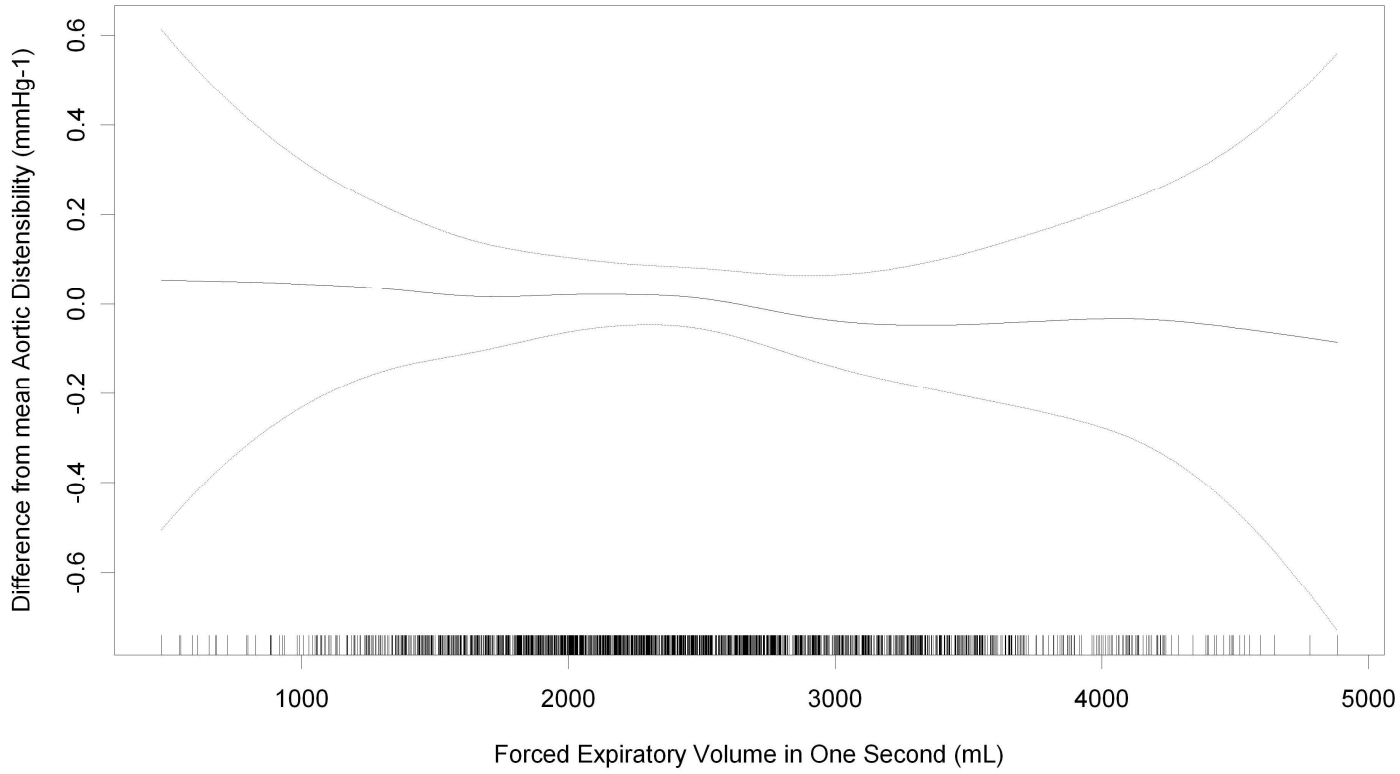

Figure 6-2 Association of proximal aortic distensibility FEV_1 (ml)

Obtained using generalised additive model of proximal aortic distensibility on FEV_1 adjusting for study site, age, race, gender, height, body mass index, heart rate, cigarette smoking status, pack years, diabetes, hypertension, educational attainment, serum low density lipoprotein, high density lipoprotein, and glucose concentration, antihypertensive therapy, lipid lowering therapy, left ventricular stroke volume and CT scanner type. Solid line=smoothed regression line, dashed lines=95% confidence intervals; vertical lines=rug plot of data points. There was no evidence of a linear association between proximal aortic distensibility and FEV_1 (p=0.43).

Since proximal aortic distensibility is comprised of a ratio, and the use of ratios as dependent variables in regression models can produce false correlations (Kronmal 1993), proximal aortic distensibility was also modelled using the change in area of the aorta as the dependent variable adjusting for minimum area of the aorta and brachial pulse pressure as independent variables. The findings were qualitatively similar.

Since cardiac MR measures of aortic distensibility estimate the central distending pressure from the brachial artery pressure, maximal cross sectional area was also modelled as the outcome measure. The findings were qualitatively similar.

6.4. Discussion

There was no evidence for an association between distensibility in the proximal ascending aorta and FEV_1 or percent emphysema in this large sample with precise measures. Nor was distensibility lower in those participants with airflow limitation compared to the remaining participants.

Previous population-based studies that have examined associations between lung function or airflow limitation and PWV are limited to two European studies of 194 and 827 middle aged men (Zureik, Benetos, et al. 2001; Bolton et al. 2009), in which associations were found, and one negative study in 678 healthy Japanese-Americans (Taneda et al. 2004). PWV has previously been found to be higher in patients with COPD than controls matched on age, sex and smoking (Sabit et al. 2007; Maclay, McAllister, Mills, Paterson, et al. 2009). All these studies employed carotid-femoral PWV which measures pulse wave transition from the aorta to the iliac artery. In Chapter 5 an association between emphysema and carotid-radial PWV was reported.

The discrepant findings as regards the associations between lung function and arterial stiffness may result from differences in the populations studied, the study design, the site at which arterial stiffness was measured, and the measures of arterial stiffness employed.

6.4.1. Differences in anatomical site of arterial stiffness

Proximal aortic distensibility measured via cardiac MR was not associated with reduced lung function, airflow limitation or percent emphysema in the MESA cohort. Cardiac MR distensibility and PWV are both well-validated measures of aortic stiffness (Oliver & Webb 2003; Laurent et al., on behalf of the European Network for Non-invasive Investigation of Large Arteries 2006), and are both associated with markers of coronary artery plaque burden (Giannattasio et al. 2007; van Popele et al. 2006), endothelial dysfunction (Gullu et al. 2006; Newby et al., with McEniery et al., Yasmin 2006), and peripheral microvascular dysfunction (Cheung et al. 2007; Mitchell et al. 2005), although only carotid-femoral PWV has been validated in longitudinal studies as a predictor of cardiovascular risk (Laurent et al., on behalf of the European Network for Non-invasive Investigation of Large Arteries 2006).

However, each measures stiffness at a different site. Carotid-femoral PWV measures stiffness regionally across the whole thoraco-abdominal aorta, carotid-radial across the aorta to the radial artery, and cardiac MR measures stiffness in one local site, in this case the ascending aorta. The proximal aorta contains a higher ratio of elastin to collagen, has less smooth muscle, and stiffens more with ageing than more distal aortic regions (Apter 1967; Duprez et al. 2007; Harkness et al. 1957; Rogers et al. 2001). Therefore, anatomical and physiological differences in the arterial regions studied, might explain why there was no association between proximal aortic distensibility and FEV_1 and airflow limitation in MESA unlike the majority of previous reports, or between proximal aortic distensibility and percent emphysema, unlike the association between carotid-radial PWV and percent emphysema reported in Chapter 5.

In 162 participants selected from the Anglo-Cardiff Collaborative Trial the strongest associations between age and aortic stiffness measured via MR were found in the abdominal aorta and the weakest in the aortic arch, while the converse was true for aortic diameter in systole. The authors postulated that the latter phenomenon might be a compensatory mechanism in the presence of increased distal aortic stiffness (Hickson et al. 2010). Therefore, we might have expected to see increased aortic diameter in patients with lower FEV_1, even if the primary mechanism for increased stiffness occurs distally.

6.4.2. Technical differences in measurement of arterial stiffness

However, PWV and cardiac MR differ considerably in the methods used to measure arterial stiffness which may also explain the discrepant findings.

Although cardiac MR allows accurate estimates of the cross-sectional area of defined arterial segments in systole and diastole, subsequent calculations of distensibility also require the distending pressure. Central pulse pressure cannot be directly measured using MR and instead is estimated from brachial pulse pressure. Use of this estimation tends to bias measures of association between ageing and distensibility towards the null (Duprez et al. 2007), and may have a similar effect on associations between aortic distensibility and FEV_1 or airflow limitation.

However, ageing-related changes such as elastin fragmentation and collagen remodelling also cause an increase in the diameter of the ascending aorta (Nichols & O'Rourke 1990), and this measure does not require any estimate of pulse pressure. Aortic cross sectional area was 55 mm^2 greater with each decade of life, but there was no association between aortic cross sectional area and either percent emphysema or FEV_1, implying that aging-like changes in the ascending aorta are not associated with reduced FEV_1, airflow limitation or increased percent emphysema (data not shown).

Moreover, in PWV measured via applanation tonometry the distance the wave-form travels is estimated from body surface measurements (e.g. sternal notch to femoral pulse), which may make it is more prone to measurement bias than cardiac MR. FEV_1 and CT measures of emphysema also relate to height and therefore bias in measurement may contribute to previously reported associations between PWV and lung function, for example if body surface area measurements systematically underestimate vessel length in taller individuals. PWV systematically overestimates arterial stiffness in older individuals as a consequence of the increased tortuosity in the abdominal aorta which is seen with ageing (Oliver & Webb 2003), and it is not known whether aorta tortuosity is affected by changes in emphysematous lungs, such as hyperinflation, although bias from body surface measurement is less likely to explain the association between percent emphysema and carotid-radial PWV.

6.4.3. Differences in populations studied

An additional consideration is that MESA participants were identified as having airflow limitation on screening spirometry, whereas subjects in the two case-control studies and in the study detailed in Chapter 5 participants were recruited from amongst patients who had presented to a clinician with symptoms suggestive of COPD as well as airflow limitation on spirometry. Individuals who presented clinically with COPD are likely to have had more co-morbidity, to have regularly used medication which can affect endothelial and vasomotor function such as beta-agonist and corticosteroids therapy, and to have experienced acute exacerbations of COPD. Therefore, the spectrum of disease among those with airflow limitation in the MESA cohort was milder than in the studies based upon patients recruited from clinical settings, which might explain the discrepant findings for emphysema severity and measures of arterial stiffness between the studies.

However, disease severity is unlikely to account for the lack of association between FEV_1 and aortic distensibility since carotid-femoral PWV has been associated with FEV_1 in studies which obtained samples from the general population (Zureik, Benetos, et al. 2001; Bolton et al. 2009). In MESA, and in the study of Japanese-Americans reported by Taneda et al (Taneda et al. 2004), in which arterial stiffness was not associated with FEV_1, smoke exposure was lower than in the two European population based studies which reported associations between PWV and FEV_1. However, this seems an unlikely reason for the discrepancy between the studies, as Zureik et al found that FEV_1 was associated with PWV even amongst never smokers (Zureik, Benetos, et al. 2001).

In MESA, participants were very well characterised in terms of cardiovascular risk factors, but even in unadjusted models proximal aortic distensibility was not associated with FEV_1 or percent emphysema, so confounding is unlikely to account for the divergent findings.

6.4.4. Limitations

A relatively large proportion of MESA participants did not have proximal aortic distensibility measures on MR; therefore selection bias cannot be entirely excluded. However, participants with and without proximal aortic distensibility measures had

similar lung function and percent emphysema values, which makes severe selection bias unlikely.

MESA excluded participants with known cardiovascular disease at baseline, which may mean participants with more severe aortic distensibility or FEV_1 are likely to have been excluded, making it more difficult to demonstrate an association between aortic distensibility and both FEV_1 and percent emphysema. However, the sample was large and measures were precise, making it unlikely that an association of an important magnitude was undetected.

MESA CT measures of emphysema were obtained from the lung fields of cardiac CT scans and therefore visualization of the lung apices was limited. Nonetheless, the CT percent emphysema measures were highly reproducible and validated (Hoffman et al. 2009). Lung function was assessed approximately 4 years after the other measures; however, the expected mean change in FEV_1 over a period of 4 years in a population-based study such as MESA is small (Jiang et al. 2008). Therefore, misclassification due to the 4-year interval is unlikely to explain the observed findings.

Spirometry was performed without administering a bronchodilator, and as such a proportion of participants with airflow limitation may have had asthma rather than COPD. However, excluding participants with asthma diagnosed before the age of 45 did not affect the findings. Moreover, none of the previous population-based studies employed post-bronchodilator measures.

6.4.5. Conclusions

There was no association between FEV_1 and ascending proximal aortic distensibility, despite the majority of previous published works reporting associations between FEV_1 and carotid-femoral pulse wave velocity. Nor was percent emphysema associated with proximal aortic distensibility, although an association between carotid-radial PWV and percent emphysema was reported in Chapter 5.

Although there were differences in population and in the method used to measure arterial stiffness, the most plausible explanation for the discrepancy in these results was that this study measured stiffness in the proximal ascending aorta, while previous studies measured stiffness across larger regions of the arterial tree.

The proximal aorta is the region of the arterial tree with most elastin and least smooth muscle (Apter 1967; Harkness et al. 1957) and is the region most affected in primary connective tissue disorders such as Marfan's syndrome and congenital bicuspid aortic valve (Adams et al. 1995; Grotenhuis et al. 2007). Therefore, the previously reported associations between FEV_1 and arterial stiffness are unlikely to be mediated by a shared susceptibility in the connective tissue of arteries and lung, at least amongst individuals without severe COPD.

Chapter 7 addresses this question further by measuring associations between lung function and measures of vascular pathology at different sites along the arterial tree.

7. Cross sectional study in multi-centre general population sample: calcification of the aorta measured by CT scanning

7.1. Introduction

In Chapter 5, an association was reported between percent emphysema and carotid-radial pulse wave velocity, a marker of arterial stiffness, in patients with COPD. Previous authors have reported associations between carotid-femoral PWV and FEV_1 in men (Zureik, Benetos, et al. 2001; Bolton et al. 2009) and increased carotid-femoral PWV in patients with COPD compared to controls matched on age, and sex (Sabit et al. 2007). More recently, carotid-femoral PWV has been found to be higher in male ex-smokers with COPD than in male ex-smokers matched on age and pack years smoking (Maclay, McAllister, Mills, Paterson, et al. 2009).

However, in a large population based sample including participants with airflow limitation there was no evidence of an association between FEV_1 or percent emphysema and reduced distensibility in the proximal ascending aorta (Chapter 6). One possible explanation for these apparently divergent findings is that the relationship between aortic stiffness and lung function, and/or emphysema, differs by anatomical site.

Arterial distensibility can be assessed at different anatomical sites along the course of the aorta using magnetic resonance imaging (Rogers et al. 2001), but distensibility was measured at only one site in MESA participants. However, aortic calcification is associated with aortic stiffness in healthy individuals and in renal disease (Guerin et al. 2000; Odink et al. 2008; McEniery et al., Yasmin & and & Maki-Petaja et al., on behalf of the Anglo-Cardiff Collaboration Trial Investigators2009), is a feature of both atheroma formation and degenerative connective tissue changes (elastocalcinosis) and was measured at various aortic sites in MESA. In addition, abdominal aortic calcification is itself a strong predictor of cardiovascular mortality (Wilson et al. 2001; Rodondi et al. 2007) yet the relationship of FEV_1 to aortic calcification has not been established.

Therefore, the aim of this chapter is to test the hypothesis that reduced FEV_1 and percent emphysema on computed tomography (CT) scans are associated with calcification of the vasculature from the ascending aorta to the iliac arteries.

7.2. Methods

Of the 3,531 participants in MESA-Lung with acceptable spirometry measures and without restriction on spirometry, 1,312 were randomly selected to have abdominal aortic calcification measures. The recruitment, study design, procedures and measurements in MESA lung, were described in Section 6.2.1.

7.2.1. Aortic calcification

CT scans of the abdomen were acquired on multidetector (MDCT) and electron beam (EBT) scans in 2002 and 2005 in a randomly selected subset of the cohort. CT images were analyzed centrally using a standard protocol by the MESA CT Reading Center. Calcification in the wall of the distal abdominal aorta in an 8 cm in length segment proximal to the aortic bifurcation was measured (Figure 1-1). Calcification was identified as a plaque of ≥1mm2 with a density of ≥130 Hounsfield units (Hu) and quantified using the Agatston scoring method (Michos et al. 2008). Calcification in the proximal abdominal aorta and each iliac artery was scored similarly.

Similar methods were used on cardiac CT scans in 2000-02 (Carr et al. 2005) to measure ascending aortic calcification and descending thoracic aortic calcification. Calcification was identified as plaque of ≥4.6 mm^3 and ≥5.5 mm^3 on EBT and MDCT respectively as previously described (Takasu et al. 2009).

7.2.2. Statistical analysis

Relative risk regression with robust standard errors (log-link and Poisson error distribution) was employed to estimate associations between relevant variables and the presence of detectable calcification. Among participants with detectable calcification the log-transformed magnitude of distal abdominal aortic calcification was modelled using linear regression. The exponentiated coefficients are presented, and may be interpreted as multiplicative (i.e. ratio) change in average distal abdominal aortic calcification. This analysis was performed for consistency with previous MESA reports examining arterial calcification, and according to guidance

approved by the MESA steering committee (Erbel et al., on behalf of the Multi-Ethnic Study of Atherosclerosis and the Investigator Group of the Heinz Nixdorf Recall Study 2008).

Sensitivity analyses were performed using emphysema measures corrected for both outside and inside air. Interactions were tested with multiplicative terms in regression models.

7.3. Results

Of the participants in the MESA Lung Study with valid spirometry measures and without restrictive lung disease, 1,312 had distal abdominal aortic CT measures. Participants with distal abdominal aortic calcification measures were very similar to those without (Table 7-1).

Table 7-1 Comparison of participants with and without distal abdominal calcification measures

	Distal abdominal aortic calcification not measured	Distal abdominal aortic calcification measured
n	2218	1312
Age, mean (SD), years	61 (10)	61 (10)
Gender – male, n (%)	1059 (47.7)	676 (51.5)
Height, mean (SD), cm	166 (10)	167 (10)
BMI, mean (SD), kg/m^2	28 (5)	28 (5)
Ethnicity, n (%)		
Caucasian	701 (31.6)	532 (40.5)
Chinese	379 (17.1)	206 (15.7)
African-American	671 (30.3)	251 (19.1)
Hispanic	467 (21.1)	323 (24.6)
Smoking status, n (%)		
Never Smoked	1045 (47.1)	624 (47.6)
Ex-smoker	877 (39.5)	490 (37.3)
Current Smoker	296 (13.3)	198 (15.1)
Pack Years, median (IQR)	18 (7-34)	18 (8-37)
Spirometry, mean (SD), %		
FEV_1 percent predicted	96 (18)	96 (17)
FVC percent predicted	98 (15)	98 (14)
FEV_1/FVC ratio	75 (9)	74 (9)
MRC Bronchitis, n (%)	160 (7.2)	114 (8.7)

	Distal abdominal aortic calcification not measured	Distal abdominal aortic calcification measured
CT percent emphysema, median (IQR), %	15 (8-25)	15 (8-25)
Asthma (self reported, aged <45)	190 (8.6)	89 (6.8)
Self reported, n (%)		
Hypertension	930 (41.9)	535 (40.8)
Diabetes	243 (11.0)	123 (9.4)
Antihypertensive medication	800 (36.1)	420 (32.0)
Lipid Lowering Therapy	341 (15.4)	207 (15.8)
BP, mean (SD), mmHg		
Systolic Blood Pressure	124 (20)	124 (19)
Diastolic Blood Pressure	71 (10)	72 (10)
Pulse Pressure	53 (16)	52 (16)
Heart Rate, mean (SD), beats/min	63(9)	63 (9)
Lipids, mean (SD), mg/dl		
LDL Cholesterol	117 (31)	118 (30)
HDL Cholesterol	51 (15)	51 (15)
Triglycerides	129 (87)	132 (80)
CRP, median (IQR), mg/L	1.76 (0.78-3.98)	1.65 (0.76-3.85)

7.3.1. Lung function and abdominal aortic calcification

Of the 1,312 participants who had distal abdominal aortic calcification measured, 903 (68.8%) had detectable calcification. Although the presence of distal abdominal aortic calcification was not associated with FEV_1 (RR 0.92; 95% CI 0.80 to 1.07; p=0.28) lower FEV_1 was associated with a greater multiplicative (ratio) increment in the extent of distal abdominal aortic calcification after adjusting for study centre,

age, sex, race/ethnicity, height, and BMI (FEV_1 one litre increment; 0.57 ratio; 95% CI 0.45 to 0.72, p<0.001). The strength of the association was attenuated but still evident after additional adjustment for cigarette smoking status, pack years, diabetes, hypertension, educational attainment, serum low density lipoprotein, high density lipoprotein, and glucose concentration, antihypertensive therapy, and lipid lowering therapy (0.76 ratio; 95% CI 0.60 to 0.97, p=0.02).

A weaker association between FEV_1 and distal abdominal aortic calcification was found amongst never smokers (n=432, 0.91 ratio; 95% CI 0.56 to 1.47, p=0.70) than amongst ex-smokers and current smokers (n=612, 0.71 ratio; 95% CI 0.54 to 0.94, p=0.02) but the confidence intervals were broad, and an interaction term for never/ever smoked and FEV_1 was not statistically significant (p-interaction=0.26).

The FEV_1/FVC ratio was also associated with the extent of distal abdominal aortic calcification after minimal adjustment, and similar trends were evident in the full model, although the associations were no longer statistically significant (Table 7-2).

Table 7-2 Multivariate Analysis – Distal abdominal aortic calcification in relation to FEV_1, FVC, the FEV_1/FVC ratio, and CT percent emphysema

Exposure (units)	Estimated multiplicative (ratio) change in distal abdominal aortic calcification (95% CI), n=903	p Value for Trend
FEV_1 (litres)		
Model 1	0.57 (0.45 to 0.72)	<0.001
Model 2	0.76 (0.60 to 0.97)	0.02
FVC (litres)		
Model 1	0.72 (0.58 to 0.91)	0.006
Model 2	0.82 (0.66 to 1.02)	0.07
FEV_1/FVC (ratio)		
Model 1	0.76 (0.67 to 0.86)	<0.001
Model 2	0.91 (0.80 to 1.04)	0.17

Similar associations between FEV_1 and vascular calcification were found in the more distal iliac arteries. In contrast, there was no evidence for an association between FEV_1 and ascending aortic calcification or descending thoracic aortic calcification (Figure 7-1). A similar pattern was found for the FEV_1/FVC ratio, but not for the FVC (data not shown).

Similar results for distal abdominal aortic calcification were obtained when participants were compared by respiratory condition. Compared to participants with normal lung function without self-reported asthma, distal abdominal aortic calcification was higher for participants with moderate airflow limitation (1.24; 95% CI 0.87 to 1.79), and higher still in those with severe airflow limitation (1.31; 95% CI 0.55 to 3.13).

7.3.2. Emphysema and aortic calcification

There was no evidence to suggest that percent emphysema was associated with extent of abdominal aortic calcification (1.05; 95% CI 0.72 to 2.06, p=0.47) in models adjusting for study site, age, race/ethnicity, gender, height, body mass index, cigarette smoking status, pack years, diabetes, hypertension, educational attainment, serum low density lipoprotein, high density lipoprotein, and glucose concentration, antihypertensive therapy, lipid lowering therapy and scanner type and protocol.

7.3.3. Sensitivity analyses

Use of percent emphysema measures corrected for outside air or airways air, or use of the 15th percentile point did not affect the results. Additional adjustment for self-reported use of bronchodilators, steroids, or methylxanthines had little impact on the results. There was no evidence for effect modification on an additive scale by gender, race/ethnicity, study site, CT scanner type or severity of airflow limitation on spirometry, nor any evidence of statistically significant departures from linearity for any of the main relationships (data not shown).

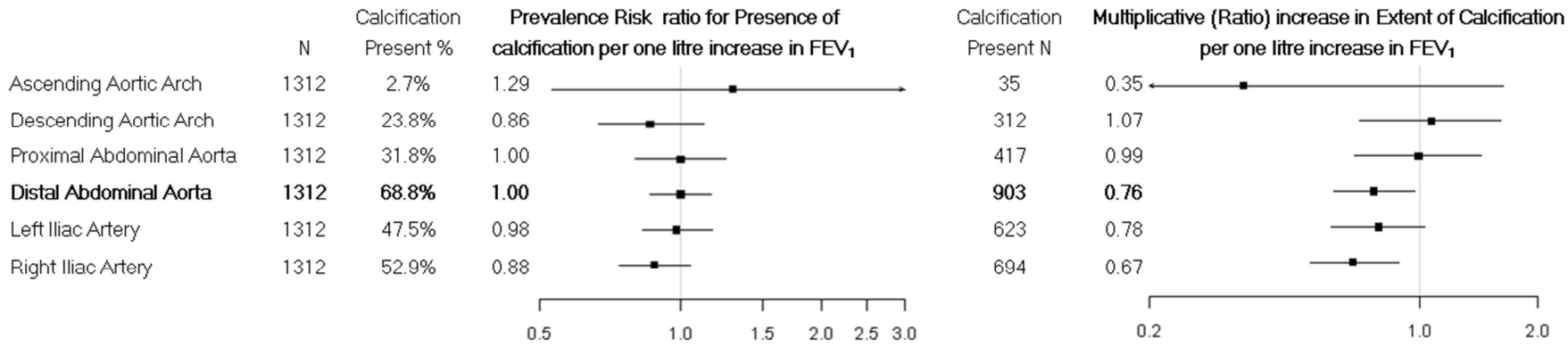

Figure 7-1 Multivariate associations of the forced expiratory volume in one second with presence and multiplicative change in aortic calcification from the proximal ascending thoracic aorta to the distal abdominal aorta and iliac arteries

7.4. Discussion

Reduced FEV_1 was associated with greater extent of calcification in the distal aorta. In contrast, reduced FEV_1 was not associated with proximal aortic calcification, consistent with the finding of no association between FEV_1 and PWV and aortic distensibility reported in Chapter 6. Furthermore, there was a graded increase in the magnitude of the association between lung function and the extent of calcification from the proximal thoracic to distal abdominal aorta.

Carotid-femoral PWV has previously been found to be associated with aortic calcification in healthy individuals, with the strongest associations found for abdominal aortic calcification (McEniery et al., Yasmin & and & Maki-Petaja et al., on behalf of the Anglo-Cardiff Collaboration Trial Investigators2009). A composite measure of arterial calcification measured at several arterial sites, including the distal abdominal aorta, has been found to be associated with carotid-femoral PWV in patients with end-stage renal disease (Guerin et al. 2000). Therefore, if aortic stiffness is truly related to reduced lung function, then the findings presented in this chapter suggest that the distal rather than proximal aorta is the likely site of the pathological vascular changes.

Moreover, like carotid-femoral PWV abdominal aortic calcification is a cardiovascular risk factor (Wilson et al. 2001; Rodondi et al. 2007). Therefore, the association between FEV_1 and aortic calcification is of interest notwithstanding aortic stiffness.

These findings may generalise to patients with COPD as, despite loss of statistical power as a consequence of categorisation, similar results for distal abdominal aortic calcification and proximal aortic distensibility were obtained when participants were compared by respiratory condition, as defined symptomatically. Therefore, pathological changes in the distal rather than the proximal aorta may be implicated in COPD.

7.4.1. Atheromatous plaques

Vascular calcification occurs in the intima in atheromatous plaques, and in the medial elastic laminae. Several previous studies have examined associations between

FEV_1 and measures of atheromatous disease (Section 1.4.1) but only two have examined measures of atheromatous disease in the abdomen/lower limbs.

In 220 male smokers from a 1914 Swedish Birth Cohort Engström et al. (2001) tested for an association between FEV_1 and the presence of sub-clinical leg or carotid atheroma (composite endpoint) in men. FEV_1 was measured via spirometry and was standardised by height. Carotid atheroma was assessed using doppler ultrasound, and leg atheroma was measured using the systolic ankle–arm pressure index. After adjusting for current tobacco consumption, hypertension (high blood pressure), diabetes and alcohol consumption, height-standardised FEV_1 was associated with atheroma burden (0.5 litre increase in FEV_1; OR 0.76 (95%CI 0.57 to 0.998). Schroeder et al. (2005) examined lung function and markers of plaque burden in 14,480 participants obtained by probability sampling in the Atherosclerosis Risk in Communities. Atheroma in the leg was identified via the ankle brachial index (ABI). FEV_1 was associated with atheroma burden in the leg measured via ABI, even amongst never smokers and after adjusting for age, gender, race, study centre, height, height-squared, and established cardiovascular risk factors.

Together with these previous studies which both measured reduced blood flow or blood pressure in the lower limbs relative to the upper, and therefore were proxies for atheromatous plaques causing stenosis in the arterial tree at any site from the descending thoracic aorta to the ankle, the current findings suggest that FEV_1 may be associated with calcified atheromatous plaque disease.

FEV_1 has previously been associated with increased CRP, circulating platelets, leukocyte and fibrinogen (Sin & Man 2003), and TNF-α, CRP and oxidised lipids are increased in COPD (Gan et al. 2004; Santus et al. 2005). CRP has been implicated in atheroma formation (Libby 2002). TNF-α causes smooth muscle cells to undergo osteoblastic differentiation and mineralisation thereby promoting calcification (Tintut et al. 2000). Oxidised lipids also promote smooth muscle cell osteoblastic differentiation, but inhibit this process in bone-derived preosteoblasts (Parhami et al. 1997), which is of particular interest since osteoporosis is inversely associated with arterial stiffness in COPD (Sabit et al. 2007). Therefore systemic inflammation and oxidative stress is one possible mechanism linking FEV_1 with aortic calcification.

7.4.2. Medial elastocalcinosis

In non-atheromatous regions of artery, a distinct calcification process occurs in elastic laminae in the tunica media (Elliott & McGrath 1994), termed medial elastocalcinosis. Medial elastocalcinosis is associated with ageing, but like atheromatous calcification is believed to be affected by inflammation and oxidative stress, and also by dysregulation of promoters and inhibitors of calcification (Atkinson 2008). Therefore, as with atheromatous calcification, systemic inflammation and oxidative stress might link FEV_1 and COPD to medial elastocalcinosis.

A distinct mechanism implicated in medial calcification is elastin degradation, as in animal models induced elastolysis causes calcification and ongoing medial elastocalcinosis (Atkinson 2008). However, it appears unlikely that the association between calcification and FEV_1 is mediated by a shared susceptibility to elastin degradation, as hypothesised in Chapter 5, for the following reasons. Firstly, percent emphysema, unlike FEV_1 and the FEV_1/FVC ratio, was not associated with calcification, secondly the calcification in the proximal aortic (the vascular region with the highest elastin) was not associated with either FEV_1, and thirdly, as reported in Chapter 6, reduced distensibility of the highly elastic proximal aorta was not associated with FEV_1 or percent emphysema.

7.4.3. Limitations

This study employed the same emphysema measures and spirometry as that described in Chapter 6, and as such the same limitations in these measures described in Section 6.4.4 apply.

MESA excluded participants with known cardiovascular disease at baseline. However, this is likely to lead to an underestimation of the strength of the association between aortic calcification and FEV_1.

Power was limited for patients with severe COPD, and caution is required in extrapolating these findings to this group. Nevertheless, there was no evidence for any departure from linearity across the range of lung function, and results comparing participants with moderate and severe airflow limitation on spirometry were consistent with those obtained measuring lung function in the full cohort.

In stratified analyses, extent of calcification was not associated with FEV_1 amongst participants who had never smoked, although the confidence interval was broad and the p-value for the interaction between FEV_1 and calcification was not significant. As discussed previously (Section 1.4.1), pack years is only an approximate measure of lifelong smoke exposure, therefore one cannot exclude residual confounding by lifelong smoke exposure as an explanation for the association between FEV_1 and calcification.

The independence of the association between FEV_1 and cardiovascular risk to cigarette smoke exposure, and to a lesser extent the associations between FEV_1 and atheroma and arterial stiffness, has been shown by demonstrating associations in never smokers (Hole et al. 1996; Schroeder et al. 2003; Schroeder et al. 2005; Zureik, Benetos, et al. 2001), and a study with a larger sample of never smokers with measures of calcification may help address this issue.

7.4.4. Conclusion

FEV_1 was associated with distal abdominal aortic calcification independently of smoking and other cardiovascular risk factors but not with distensibility or calcification of the proximal aorta. These findings suggest that increased aortic stiffness and related atherosclerotic risk in reduced lung function may be mediated by changes in the distal aorta.

8. Discussion

As discussed in Section 1.2, cardiovascular mortality is common in people with COPD, and FEV_1 is a well established predictor of cardiovascular mortality and morbidity independent of established cardiovascular risk factors, even amongst never smokers. FEV_1 may be a broad marker of poor health, or as suggested by some authors (Sin & Man 2003; MacNee et al. 2008), COPD may have a causal relationship with cardiovascular morbidity and mortality.

The associations described between FEV_1, COPD and cardiovascular health led to three broad hypotheses that were addressed in this thesis.

1 FEV_1 is a potentially useful prognostic marker in patients undergoing cardiac surgery.

2 Exacerbation of COPD partly accounts for the association between cardiovascular morbidity and mortality and COPD/airflow limitation, and acute coronary syndrome is common in exacerbation of COPD.

3 Pathological changes in the systemic vasculature partly mediate the association between COPD/ reduced FEV_1 and cardiovascular morbidity and mortality.

8.1. FEV_1 and cardiac surgery

In Chapter 2, an inverse association between FEV_1 and both mortality and increased length of hospital stay was reported. Moreover, the association was independent of existing prognostic markers used in cardiac surgery, and improved discrimination and calibration when added to the current most widely used prognostic tool, the euroSCORE. This finding is of interest because risk prediction in cardiac surgery is important for clinical decision making, auditing and service planning. As such, the predictive value of FEV_1 should be examined in a confirmatory dataset, preferably from more than one centre, and evaluated for inclusion in future risk prediction tools.

Interestingly, the associations between FEV_1 and both mortality and length of stay were broadly linear. Previous studies examining FEV_1 in population settings also found that FEV_1 predicted adverse events in a broadly linear fashion. Therefore, there appears to be no threshold above which a higher FEV_1 does not predict a lower

risk of adverse outcomes. Consequently these findings argue against a specific COPD "effect" on cardiovascular health, and also imply that FEV_1 may be a broad marker of poor health.

8.2. Exacerbation of COPD and acute coronary syndrome

As discussed in Section 1.5.2, two observational studies, both of which used routine data, reported that cardiovascular risk may be increased acutely in patients with COPD during acute exacerbations, and current COPD guidelines do not address the investigation or management of acute coronary syndrome in patients with acute exacerbation of COPD.

The findings from Chapter 3 suggest that there is no clinical consensus amongst Scottish Respiratory Consultants regarding whether and how patients with COPD should be investigated for the presence of acute coronary syndrome, or as to the utility of clinical investigations such as serum troponin or serial electrocardiograms in exacerbation of COPD.

The survey also found that the majority of respondents believed that features in the chest pain history could be used to risk stratify patients with exacerbation of COPD and chest pain to identify whether it was appropriate to investigate patients with exacerbation of COPD for acute coronary syndrome. However, in patients presenting with chest pain rather than acute exacerbation of COPD, current guidelines suggest that chest pain character is only of limited prognostic value in uncomplicated chest pain (NICE 2010),

In this survey there was no clear clinical consensus regarding the investigation of acute coronary syndrome in this survey, and patients with exacerbations therefore may be at risk of both under-diagnosis and over-diagnosis.

The case-series reported in Chapter 4 found that 2.5% of patients admitted to hospital with exacerbation of COPD had chest pain, serial electrocardiogram changes and raised troponin. Cardiovascular risk factors were also common in this patient group, and exacerbation itself may acutely increase the risk of acute coronary syndrome in patients with COPD (Huiart et al. 2006; Donaldson et al. 2010). Therefore, although non-coronary mechanisms such as right heart strain and acidosis are likely to cause

the majority of cases of raised troponin in exacerbation of COPD, coronary mechanisms are also implicated.

Furthermore, approximately 20% of patients with exacerbations had chest pain with features usually considered 'high-risk' for acute coronary syndrome (eg exertional, radiating to arms or jaw) and no 'low-risk' features, and half of these also had raised troponin. Moreover, raised troponin was not associated with chest pain, or serial electrocardiogram changes.

Therefore, the high prevalence in exacerbation of COPD of raised troponin, chest pain conventionally considered suggestive of ischaemia, and abnormal ECGs was shown to represent a considerable diagnostic difficulty, and the approach advocated by the majority of respondents in the survey reported in Chapter 3, risk stratifying patients with exacerbations on the basis of features in the chest pain history, appears problematic.

The case-series described in Chapter 4 did not sample patients consecutively, was relatively small, and ECGs were not obtained in controlled conditions. However, while larger observational studies may more precisely estimate the prevalence of raised troponin, chest pain and ECG changes, and may better identify further patient characteristics which are associated with raised troponin, they are unlikely to identify which clinical features are also indicative of acute coronary artery thrombosis. Indeed, given the clinical complexity, only experimental studies (eg clinical trials of secondary prevention strategies) are likely to address the question of how best to manage patients with exacerbation of COPD and raised troponin. Such trials may be justified given the high proportion of patients with raised troponin, and in view of the previous report in patients with severe exacerbations in which mortality was considerably higher when troponin was raised (Baillard et al. 2003).

8.3. FEV_1 and COPD and vascular pathology

8.3.1. Arterial stiffness

As discussed in Section 1.4.2 several studies have examined arterial stiffness in relation to COPD and FEV_1. Two case-control studies found that carotid-femoral PWV was raised in COPD compared to controls, and two European studies in men

recruited from the community found that carotid-femoral PWV was associated with FEV_1. However, FEV_1 was not associated with carotid-femoral PWV in a population-based study of Japanese-Americans. This thesis employed two measures of arterial stiffness, carotid-radial PWV in patients with COPD, and aortic distensibility on MR in a population-based sample.

In Chapter 5, an association between carotid-radial PWV and percent emphysema was reported. This finding supports the hypothesis that arterial stiffness is associated with lung function and increased in COPD, and the hypothesis that a shared susceptibility in the connective tissues of artery and lung might be a mechanism linking the two processes.

However, this finding was in a selected population, and used a technique which measured arterial stiffness predominantly across the more muscular brachial artery, rather the central arteries. To address these deficiencies, the association between distensibility of the highly elastic ascending proximal aorta and both FEV_1 and percent emphysema was examined in a group obtained from random sampling of the general population in 6 US centres (the MESA study), the results of which were reported in Chapter 6.

FEV_1 was not associated with aortic distensibility, nor was percent emphysema associated with aortic distensibility. Therefore, the findings reported in Chapter 6 did not confirm the results reported in Chapter 5 examining carotid-radial PWV in patients with COPD, nor do they confirm the previous reports that FEV_1 is associated with aortic stiffness.

MESA performed very comprehensive assessments, allowing adjustment for a wider range of potential confounders than in previous studies. Nevertheless, in unadjusted analyses aortic distensibility was not associated with FEV_1 or with percent emphysema, so uncontrolled confounding is unlikely to account for the discrepant findings.

The most plausible reason for the discrepant findings between MESA and previous reports is the measures used. Previous case-control studies comparing patients with COPD to healthy controls, and cross-sectional studies reporting associations with FEV_1 in wider populations, employed carotid-femoral PWV to measure arterial

stiffness. Carotid-femoral PWV is more widely used than MR aortic distensibility, has been shown to predict adverse cardiovascular outcomes longitudinally (Laurent et al., on behalf of the European Network for Non-invasive Investigation of Large Arteries 2006) and as the measurement is performed across a larger vascular area, it is likely to be more sensitive. However, aortic distensibility is also a validated measure of arterial stiffness, and is less vulnerable to measurement bias than PWV (Oliver Webb). Moreover, the sample in MESA was very large, making it unlikely that the study was underpowered to detect an important association.

PWV relies on body surface measurements to estimate the length of arteries. FEV_1 is strongly associated with height, raising the possibility that bias in measurements may account for the previously described associations between FEV_1 and carotid-femoral PWV. Aortic distensibility measured on MR does not employ body surface measurements, and was not associated with FEV_1. Similarly, in the Copenhagen City Heart Study augmentation index, a measure of systemic arterial stiffness derived from the shape of the pulse wave-form at the radial artery, was only very weakly associated with FEV_1 (personal communication, Dr Julie Janner, Copnehagen, Denmark). If height and body surface measurements are overestimated then FEV_1 adjusted for height (or FEV_1 percent predicted) will be underestimated whereas carotid-femoral PWV will be overestimated. The converse is also true. Therefore, any error in measurement (eg operator under/over reading) will tend to produce a spurious negative association between FEV_1 percent predicted (or FEV_1 height adjusted) and PWV. Therefore measurement error may at least partly account for the previously reported associations between FEV_1 and PWV. Regional aortic stiffness can be measured using ultrasound and MR, and future studies employing these measures may help determine whether FEV_1 is associated with aortic stiffness.

8.3.2. Calcification

Associations between calcification at several arterial sites from the ascending aorta to the iliac arteries were examined in Chapter 7. Calcification in the distal abdominal aorta was strongly associated with FEV_1, but not with percent emphysema. Neither percent emphysema nor FEV_1 was associated with calcification in the more proximal regions of the arterial tree.

These findings suggest that if systemic vascular changes are related to FEV_1, the distal rather than proximal aorta is more likely to be involved, although there was less calcification proximally, and the study may have been underpowered to detect an association in the more proximal aorta. Nevertheless, the relative sparing of the proximal aorta implies that a shared susceptibility in the connective tissue of artery and lung, as hypothesised in Chapter 5 is less likely.

Vascular calcification of the aorta occurs in the intima in atheromatous plaques and in the media as elastocalcinosis, the calcification observed could relate to either. As discussed in Section 1.4.1 several studies have examined associations between FEV_1 and measures of atheroma, with variable results. Two previous studies have reported associations between measures of atheroma in the circulation supplying the lower limbs using functional measures, and this study supports these findings by demonstrating calcification in the distal abdominal aorta in relation to FEV_1 which may be caused by atheroma.

However, the association between abdominal aortic calcification and FEV_1 was attenuated by adjusting for potential confounders, particularly by adjusting for smoking status and pack years, although it remained statistically significant. Pack years is based upon patient recall over decades, and is therefore an inherently imprecise measure of lifetime cigarette smoke exposure. As such, residual confounding might explain the observed association. To address this issue this analysis were repeated amongst never smokers. The estimated co-efficient was in the same direction but was severely attenuated, and was not statistically significant.

This issue of residual confounding by lifelong smoke exposure applies equally to the findings from Chapters 5 and 7, and indeed is a limitation common to observational studies examining factors related to cardiovascular risk in COPD. Even in studies where there is careful matching on pack years smoking, there may be differential recall of previous smoke exposure between patients with COPD and controls, resulting in similar pack years, but different cigarette smoke exposure histories.

In population-based studies examining FEV_1 and cardiovascular risk, atheroma and arterial stiffness, sun-group analyses amongst never smokers were performed (Hole et al. 1996; Schroeder et al. 2003; Schroeder et al. 2005; Zureik, Benetos, et al.

2001). However, people with COPD are smokers and ex-smokers almost by definition, and smoking may be a necessary component cause rather than a confounder linking cardiovascular risk to COPD. Consequently, observational studies examining the association of various cardiovascular risk measures and mechanisms to COPD such as vascular stiffness and endothelial function are necessarily limited.

Consequently, additional case-control studies demonstrating differences in vascular measures, including endothelial dysfunction, arterial stiffness and atheroma measures, between patients with COPD and controls are likely to add little to the current literature. Population based studies examining associations between FEV_1 and vascular measures amongst never smokers may do so, but if null are likely to be difficult to interpret because COPD largely a disease of former and current smokers. A recent randomised controlled trial in patients with rheumatoid arthritis found that infliximab therapy (monoclonal drug therapy with anti-TNF-α activity) caused reduced systemic inflammation and reduced carotid-femoral PWV (Wong et al. 2009), and future studies attempting to definitively address cardiovascular risk in COPD will also need to adopt experimental designs in order to demonstrate causal relationships between airflow limitation and COPD and systemic vascular pathology.

8.4. Conclusion

In summary, this thesis demonstrated that FEV_1 is associated with higher mortality and prolonged length of hospital stay in patients undergoing cardiac surgery. It also demonstrated that the high prevalence of chest pain and raised troponin pose a diagnostic problem in patients with exacerbation of COPD. Finally, evidence was presented suggesting that FEV_1 is associated with systemic vascular pathology, calcification in the distal aorta.

9. References

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